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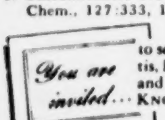

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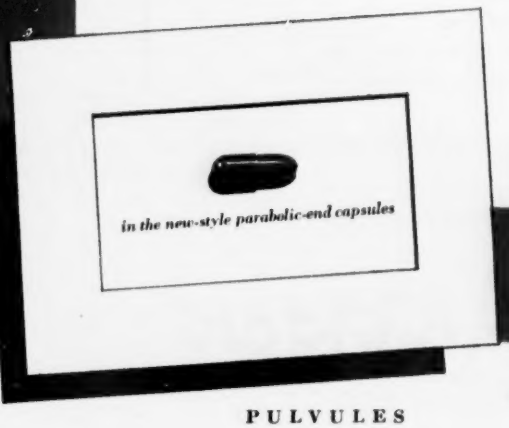

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Volume 249 AUGUST 6, 1953 Number 6

THE HEART IN I^{131}-INDUCED MYXEDEMA*

Comparison of the Roentgenographic and Electrocardiographic Findings before and after the Induction of Myxedema

GEORGE S. KURLAND, M.D.,† ROLAND E. SCHNECKLOTH, M.D.,‡ AND A. STONE FREEDBERG, M.D.§

BOSTON

STUDIES of the cardiovascular system in spontaneous myxedema have demonstrated an increased size of the cardiac silhouette, diminished force of cardiac contraction, decreased cardiac output and velocity of blood flow, diminished plasma and total blood volumes and lowered voltage of the electrocardiogram.[1-7] There is considerable difference of opinion regarding the clinical significance of these changes; in most cases, cardiac function remains adequate. The "myxedema heart" in the sense of a condition precipitating congestive heart failure, as described by Zondek[2] and Fahr,[8] occurs rarely.

The early effects of hypothyroidism, induced by surgical total thyroidectomy, on the size of the heart and pattern of the electrocardiogram have previously been described.[9] The recent availability of I^{131} and the demonstration of the therapeutic effectiveness of I^{131}-induced hypothyroidism in euthyroid patients with intractable angina pectoris and congestive heart failure have afforded the opportunity of examining the effects of prolonged controlled hypothyroidism on the cardiovascular system. This report describes the changes in the size and configuration of the cardiac silhouette and the variations in the electrocardiograms and presents a correlation of these changes with alterations in the clinical status of cardiac patients, two to fifty-three months after the development of I^{131}-induced myxedema.

MATERIAL AND METHODS

Pertinent identifying data are shown in Tables 1, 2 and 3. All patients were euthyroid before treatment; persistent hypothyroidism was produced in each case by one or more doses of I^{131}. The level of hypometabolism was controlled by administration of small doses of desiccated thyroid (6 to 90 mg.). The duration of hypometabolism ranged from two to fifty-three months and averaged twenty-seven months.

Radiologic examination, which was carried out in 27 patients (Tables 1, 2 and 3), included serial 7-foot roentgenograms of the chest taken every two to six months and, in some cases, repeated fluoroscopy. In each film the transverse cardiac diameter and the internal thoracic diameter were measured. In addition, the serial x-ray films of each patient were evaluated from the standpoint of alterations in the contours of the left and right borders of the heart, the relative size of the heart chambers and the volume of the vascular pedicles. Comparison was made only when films showed similar positioning of the subject and comparable levels of the diaphragm.

Deflections of the standard leads, augmented unipolar limb leads, and six precordial V leads of serial electrocardiograms were studied in 28 patients; measurement was made of the maximal depth of Q and S waves, and maximal height of P, R and T waves in all leads. Correction was made for errors in standardization. The duration of the PR, QRS and QT intervals was also determined. The QT interval was not regarded as prolonged unless it was 20 per cent above predicted values as calculated by Bazett's[10] formula. The effect of medications was considered in the evaluation of variations in configuration of the tracings.

The data obtained from examination of x-ray films and electrocardiograms were correlated with the clinical state, and simultaneous observations of the serum cholesterol, the basal metabolic rate, the thyroid uptake of tracer doses of I^{131} and, in some cases, determination of serum protein-bound iodine. The methods employed in the clinical and laboratory evaluation of such patients before and during myxedema have been described previously.[1]

*From the Medical Service and Medical Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard University Medical School.

This work was carried out under Contract No. AT (30-1)-916 between the Atomic Energy Commission and the Beth Israel Hospital and was also aided in part by a contract between the Office of Naval Research, Department of the Navy and Beth Israel Hospital, Harvard (NR 117-294).

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Results

Radiologic Changes in Heart Size in Patients with Angina Pectoris

The serial chest films of 19 patients with intractable angina pectoris were studied. Tables 1, 2 and 3 summarize the relation of alterations in the cardiac silhouette to the basal metabolic rate, serum cholesterol level and therapeutic result attained after I^{131}-induced hypothyroidism. The observations presented are representative of a much larger body of data obtained in each case. Laboratory and clinical evidence of hypometabolism appeared in each case one to ten months after the initial dose of I^{131}.

Eleven of the 19 patients (58 per cent) had no permanent significant change (Fig. 1) in configuration and size of the heart after two to forty-eight months of hypothyroidism (average, thirty-one months); 10 of the 11 (Cases 1-11) experienced striking or significant relief of angina pectoris after induction of hypometabolism; the pretreatment cardiac diameter was within normal limits in 3 and above normal in 8. The transverse cardiac diameter was decreased 0.6 to 1.1 cm. after I^{131} (Fig. 2) in 3 of these cases (Cases 4, 8 and 10). In 3 patients (Cases 2, 6 and 9) clinical improvement for the initial two or three years of hypometabolism was followed by an exacerbation of angina pectoris. No concomitant significant cardiac enlargement was observed. A transient increase of the transverse cardiac diameter of 0.5 cm. or more was seen in 3 patients (Cases 1, 2 and 10) on one film at some time after the onset of hypometabolism. Subsequent films showed, in each case, a return of the cardiac silhouette to its pretreatment configuration; the change was not related to variation in thyroid dosage.

In 2 of the 19 patients (Cases 12 and 13), no enlargement of the heart was observed for twenty-

Table 1. *Effect of I^{131}-Induced Hypothyroidism in Cases 1-9.*

Case No.	Sex	Age	Additional Diagnosis	Duration of Angina Pectoris before I^{131} Therapy	Duration of Hypometabolism after I^{131} Therapy	Transverse Cardiac Diameter	Basal Metabolic Rate	Serum Cholesterol	Thyroid Medication	Therapeutic Result	Over-all Changes in Cardiac Silhouette
		yr.		yr.	mo.	cm.	%	mg./100 cc.	mg./day		
1	M	41	Prior myocardial infarction	1	—	12.6	−10	328			
					2	12.6	−26	1023			
					7	15.1	—	692	12	Striking improvement	None
					12	12.2	−24	814	30	Striking improvement	
					43	12.6	−31	602	30	Striking improvement	
2	M	62	Prior myocardial infarction and pulmonary edema; hypertension.	3	—	15.7	−15	200			
					1	14.8	−17	500			
					9	16.2	−19	302	12	Striking improvement	None
					31	15.5	−24	333	12	Good	
					43	15.5	−23	311	12	Good	
3	M	38	2 prior myocardial infarctions; episodes of coronary failure.	2	—	14.9	− 3	280			
					1	14.0	−31	779			
					11	15.1	—	375	24	Striking improvement	None
					17	14.7	−25	437	30	Striking improvement	
					41	14.3	−27		30	Striking improvement	
					47	14.9	−27		30	Excellent	
4	M	60	Probable prior myocardial infarction	10	—	13.2	−10	347			Definite decrease
					1	13.0	−26	674			
					7	12.1	−23		12	Striking improvement	
					24	11.9	−22		12	Striking improvement	
5	M	44	Probable prior myocardial infarction	5	—	*	−11	352			
					30		−24		18–48	Striking improvement	None
6	M	46	Prior myocardial infarction	¾	—	13.6	−12	325			
					6	13.2	−30	575	30	Excellent	None
					20	13.5	−30	333	30	Excellent	
					25	13.5		381	30	Excellent	
7	M	48	2 prior myocardial infarctions	3	—	14.7	± 0	499			
					1	13.6	−11	602		Excellent	None
					14	14.6	−24	385	18	Excellent	
8	M	61	Prior myocardial infarction	1½	—	14.4	+ 4	220			
					1	14.0	−22	381			
					5	14.7	−28	402	12	Excellent	None
					11	13.6	−31	364	30	Excellent	
					23	13.6	− 7	230	30–45	Excellent	
					29	13.5	−14	250	30–45	Good	
9	M	69	2 prior myocardial infarctions	2½	—	14.1	− 6	275			
					7	14.4	−20	618	15	Good	None
					22	14.7	−17	550	30	Fair	
					33	14.6	−14	386	30	Fair	
					38	14.7	−21	350	30	Negligible	

*Mensuration not feasible.

six and thirty-eight months of hypothyroidism, during which a good or excellent therapeutic result had been attained. Cardiac enlargement was subsequently noted during an exacerbation of angina pectoris in Case 12 and during the development of congestive heart failure in Case 13.

Definite and progressive enlargement of the cardiac silhouette accompanying myxedema was observed in 6 of the 19 patients, or 32 per cent (Cases 14-19); some degree of cardiac enlargement had been noted before treatment in all but 1. I^{131} therapy was considered worth while in only 1 of these (Case 14), who experienced moderate relief of angina pectoris. No relation could be established between the degree of alteration in cardiac size and the degree of myxedema. Administration of small doses of thyroid to these patients was accompanied by slight decreases in heart size in some, and by the persistence of progressive cardiac enlargement in others.

TABLE 2. *Effect of I^{131}-Induced Hypothyroidism in Cases 10-19.*

Case No.	Sex	Age	Additional Diagnosis	Duration of Angina Pectoris before I^{131} Therapy	Duration of Hypometabolism after I^{131} Therapy	Transverse Cardiac Diameter	Basal Metabolic Rate	Serum Cholesterol	Thyroid Medication	Therapeutic Result	Over-all Changes in Cardiac Silhouette
		yr.		yr.	mo.	cm.	%	mg./100 cc.	mg./day		
10	M	69	2 prior myocardial infarctions	3	—	14.1	−6	370			
					1	15.1	−23	388	6	Excellent	None
					2	13.5	−21	479	6	Excellent	
11	M	57	—	9	—	16.0	−4	316			
					3	16.1	−26	384			
					6	16.6	−22	370		Negligible	None
					41	16.8	−21		30	Negligible	
12	F	47	Hypertension (post-sympathectomy)	6	—	13.9	+8	422			
					1	14.1	−21	634	6	Excellent	Definite increase
					17	14.0	−15	497	6		
					26	14.4	−21	451	6	Negligible	
13	M	65	Prior myocardial infarction; diabetes mellitus.	1½	—	13.5	*	305			
					1	13.6		630	12		
					6	13.5		360	18	Good	Definite increase
					17	13.9		550	18	Good	
					38	14.3		542	18	Negligible	
14	M	58	2 prior myocardial infarctions	1½	—	12.6	+2	307			
					6	15.0	−11	386	6	Good	Definite increase
					12	14.6	−18	350	6	Fair	
					48	15.2	—	—	6	Fair	
15	M	60	Prior myocardial infarction; diabetes mellitus; ? central-nervous-system syphilis.	6	—	14.4	−4	341			
					1	15.2	−7	376	6	Negligible	Definite increase
					7	15.7	−30	506	6	Negligible	
					19	16.5	−22	412	6	Negligible	
16	F	59	Prior myocardial infarction; hypertension.	4	—	13.7	−12	210			
					1	14.8	−43	431	12	Negligible	Definite increase
					20	14.8	−18	403	60	Negligible	
					46	15.8	−32	401		Negligible	
17	M	61	—	6	—	15.3	−6	250			
					1	15.2	−19	328			
					8	15.3	−27	413	90	Negligible	Definite increase
					11	16.3	−35	223	90	Negligible	
					25	17.0	−25	375	90	Negligible	
					34	15.7	+3	189	90	Negligible	
					47	17.0	−6	184	90	Negligible	
18	M	56	Diabetes mellitus	4	—	14.7	−8	297			Definite increase
					5	15.4	−21	398	12	Negligible	
					16	16.2	−23		15	Negligible	
19	M	55	Prior myocardial infarction	9	—	13.6	±0	309			
					1	14.7	−17	453		Negligible	Definite increase
					8	14.8	−15	401	6	Negligible	

*Mensuration not feasible.

Radiologic Changes in Heart Size in Patients with Congestive Heart Failure

The serial chest x-ray films of 6 patients with congestive heart failure were studied after I^{131}-induced hypothyroidism (Table 3). The films of 4 of these were suitable for measurement of the transverse cardiac diameter. In none was hypometabolism accompanied by progressive cardiac enlargement.

Case 20, with severe chronic congestive heart failure following multiple myocardial infarctions, experienced striking clinical improvement after induction of myxedema. After six months of hypometabolism, the transverse cardiac diameter had diminished by 3.1 cm. Fourteen months later the size of the heart gradually began to increase, but never reached its pretreatment size. After two and a half years of hypometabolism and clinical improvement, he suffered increasing angina pectoris, which culminated in an acute myocardial infarction and death.

In Case 22, with rheumatic heart disease and chronic congestive failure, a good initial clinical response to I^{131} therapy was noted. The heart did not increase in size until shortly before death from pulmonary edema, eighteen months after the onset of hypometabolism.

In the other 2 patients (Cases 21 and 23), no significant change in heart size or configuration was observed after twenty-nine and fifty-three months of hypothyroidism. One had experienced striking clinical improvement; the other evidenced no worthwhile therapeutic effect.

Accurate measurements of cardiac size could not be made from the x-ray films of an additional 2 patients with congestive heart failure because the cardiac borders extended to the lateral chest wall, or were obscured by pleural effusion or pulmonary congestion. Serial films of these patients were reviewed, and, with the aid of repeated fluoroscopy, an estimate was made of significant alterations in cardiac configuration and size. One patient (Case 24), was a forty-four-year-old woman with a past history of rheumatic heart disease and incapacitating congestive heart failure for seven years. On x-ray examination before I^{131} therapy, the transverse cardiac diameter was approximately 18.3 cm., with marked left and right dilatation of the heart borders, and posterior dilatation of the left atrium. Definite clinical improvement persisted for nineteen months after therapy. Despite the presence of moderate hypothyroidism there was no significant change in the appearance of the cardiac silhouette. Two years after I^{131} treatment there was an exacerbation of the symptoms of congestive heart failure; at this time, shortly before her death, there was a slight generalized increase in size of the heart.

The second patient (Case 25) was a thirty-year-old man with chronic rheumatic heart disease, mitral and aortic stenosis and insufficiency, chronic decompensation for twelve years and severe congestive heart failure of nine months' duration unresponsive to usual therapeutic measures. Pretreatment x-ray examination revealed a huge heart with marked dilatation of the right and left ventricles and dilatation of both atria; accurate measurement of size was not possible. His condition became progressively worse; x-ray films showed increasing dilatation of the left atrium, a dilated aorta and vena cava, bilateral hydrothorax and pulmonary congestion. Hypothyroidism developed five months

TABLE 3. *Effect of I^{131}-Induced Hypothyroidism in Cases 20-27.*

Case No.	Sex	Age	Additional Diagnosis	Duration of Decompensation before I^{131} Therapy	Duration of Hypometabolism after I^{131} Therapy	Transverse Cardiac Diameter	Basal Metabolic Rate	Serum Cholesterol	Thyroid Medication	Therapeutic Result	Over-All Changes in Cardiac Silhouette
		yr.		*yr.*	*mo.*	*cm.*	%	*mg./100 cc.*	*mg./day*		
20	M	46	Hypertensive and arteriosclerotic heart disease; 2 prior myocardial infarcts; chronic renal disease.	1½	—	21.4	± 0	255			Definite decrease; then gradual increase.
					1	20.7	*	455			
					6	18.3	—	434		Striking improvement	
					14	18.6	—	420			
					20	19.9	—	606	12	Striking improvement	
					31	19.6	—	326	12	Negligible	
21	F	59	Arterial hypertension; previous thyrotoxicosis.	1½	—	13.5	+20	213			
					3	13.0	−17	404		Striking improvement	None
					6	14.4	+3	322	90	Striking improvement	
					21	13.5	−12	324	90	Striking improvement	
					29	13.7	− 8	412	90	Striking improvement	
22	M	45	Rheumatic heart disease; mitral and aortic stenosis and insufficiency.	2	—	14.9	−11	225			
					1	14.8	−23	320			Terminal increase
					8	15.1	−21	339	18	Good	
					18	15.9	−27	406	18	Negligible	
23	F	47	Rheumatic heart disease; mitral stenosis and insufficiency; pulmonary emboli.	17	—	16.1	− 4	210			
					1	16.1	−19	331	12		
					15	15.1	−27	302	15	Negligible	None
					21	16.4		259	15	Negligible	
					33	15.6		336	30	Negligible	
					53	15.0			30	Negligible	
24	F	46	Rheumatic heart disease; mitral and aortic stenosis and insufficiency; pleural effusion; ascites.	7	—	*	+5	220			
							−22	400	6-12	Good	Terminal increase
					17				6-12	Negligible	
					22						
25	M	30	Rheumatic heart disease; mitral aortic stenosis and insufficiency	9	—	*	+3	185	—	Striking improvement	Distinct decrease
					7		−24	343	—		
					19		−28	310	—	Striking improvement	
26	M	72	Arteriosclerotic heart disease; aortic stenosis and insufficiency; hypertension.	8	—	16.0		220			Definite increase
					6	20.3	*	399	†	Striking improvement	
					15	21.1		325		Striking improvement	
					24	19.9		382		Striking improvement	
					26	20.8		383		Striking improvement	
27	M	59	Severe angina pectoris; hypertension; chronic pyelonephritis; cerebrovascular accident.	2	—	16.2	+3	178	—	Good	
					6	16.7	−18	482	15	Good	
					12	16.4	—	386	15	Good	Definite increase
					19	17.0	−19	421	15	Good	
					47	17.3	—	—	15	Good	

*Accurate measurement not feasible.
†Thyroid ordered but not taken.

after the initial dose of I^{131}. Concomitantly, there was evidence of marked clinical improvement and the patient, previously incapacitated, returned to work. After seven months of hypometabolism the lung fields were clear, the pleura dry, and the left atrium smaller on x-ray examination. Twelve months later the pulmonary vessels were normal in caliber, the aorta and vena cava were narrow, and the left atrium was probably smaller although still tremendously dilated. At this time, twenty-four months after the initial dose of I^{131}, the basal metabolic rate averaged -28 per cent and the serum cholesterol was 310 mg. per 100 cc. The patient failure and recurrent acute pyelonephritis. Induction of myxedema by I^{131} was followed by a noticeable improvement of angina pectoris and congestive heart failure. During forty-seven months of hypometabolism, the transverse cardiac diameter increased 1.1 cm. Although the patient has had two cerebrovascular accidents, there has been no recurrence of angina pectoris and only recent recurrence of congestive heart failure.

Electrocardiographic Changes in 28 Patients with Chronic Cardiac Disease

The electrocardiograms of 21 patients with angina pectoris and 7 patients with congestive heart failure

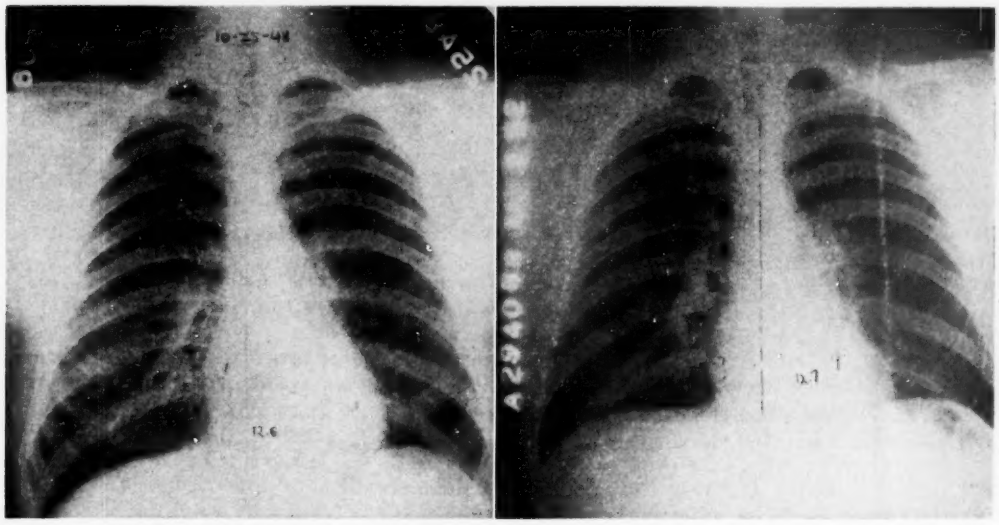

FIGURE 1. *Cardiac Silhouette before (Left) and Forty-Three Months after (Right) the Induction of Hypometabolism in Case 1.*

There has been no change in the size of the heart.

was moderately hypothyroid, but symptoms were insufficient to require thyroid medication.

Radiologic Changes in Heart Size in Patients with Both Angina Pectoris and Congestive Heart Failure

In 2 patients, with both intractable angina pectoris and chronic congestive heart failure, I^{131} therapy was followed by progressive and marked cardiac enlargement. In 1 (Case 26) induction of myxedema was accompanied by striking clinical improvement, with remission of both angina pectoris and congestive heart failure for twenty-four months. Although frank myxedema developed, the patient refused to take thyroid as ordered. Progressive cardiac enlargement with a 5.1-cm. increase of the transverse cardiac diameter occurred (Fig. 3). Nevertheless, cardiac improvement was maintained.

The second patient (Case 27) had severe hypertension, angina pectoris, chronic congestive heart

were studied before and after induction of hypometabolism with I^{131}. The electrocardiograms taken before therapy showed abnormal patterns consistent with prior myocardial infarction, bundle-branch block or hypertrophy of the left ventricle in 22 patients; tracings were abnormal, but not diagnostic, in 5, and were normal in only 1 patient.

The interpretation of the electrocardiogram after I^{131} therapy was complicated by alterations due to varying degrees of digitalization and possible progression of the underlying myocardial disease. The most pronounced changes in the electrocardiogram were observed at the lowest level of metabolism and could be attributed to myxedema. As in spontaneous myxedema,[2, 7, 12, 13] these changes consisted of lowering of voltage of the QRS complexes and, less frequently, the P waves, and flattening or inversion of the T waves. The QT interval, if slightly above normal, tended to de-

crease. Thyroid was administered and the dosage adjusted so as to maintain in each patient a level of hypometabolism affording the maximum relief from the cardiac disease and minimum discomfort sisted. Thereafter, despite months or years of hypometabolism, there was no progression of electrocardiographic changes, and surprisingly little alteration in the basic electrocardiographic pattern

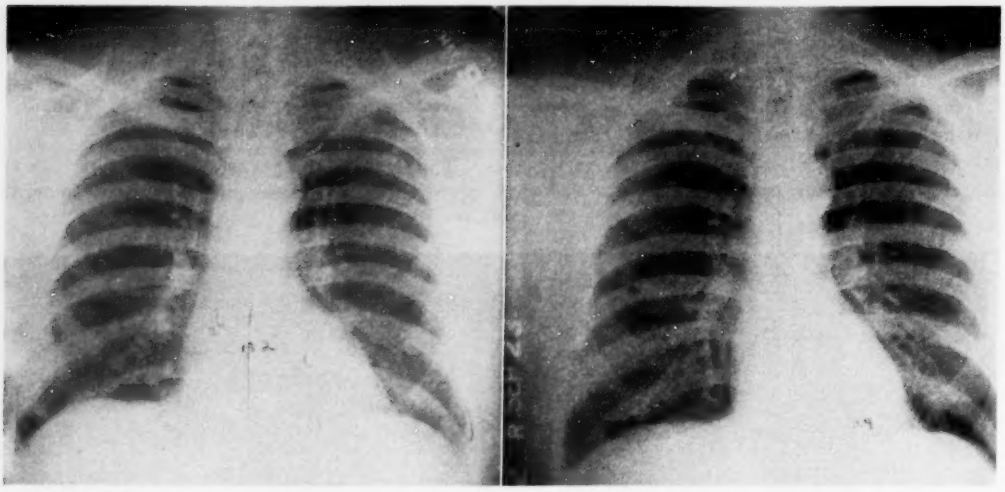

FIGURE 2. *Cardiac Silhouette before (Left) and Twenty-Four Months after (Right) the Induction of Hypometabolism in Case 4.*
The transverse diameter of the heart has decreased 1.3 cm.

from myxedema. At a metabolic level of -15 to -25 per cent, electrocardiographic alterations due to myxedema regressed and, in some cases, com-

DISCUSSION

Increase in the size of the heart is frequently found in cases of spontaneous myxedema.[1, 14, 15]

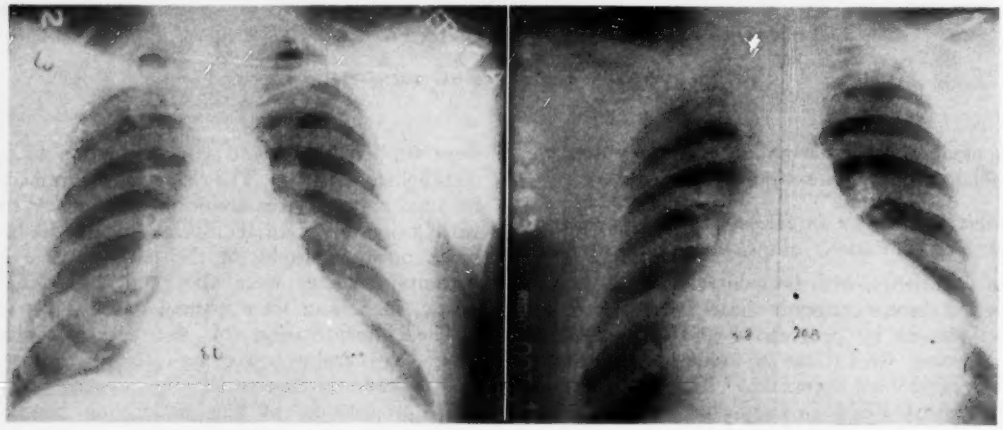

FIGURE 3. *Cardiac Silhouette before (Left) and Twenty-Six Months after (Right) the Induction of Hypometabolism in Case 26.*
The transverse diameter of the heart has increased 4.8 cm.

pletely disappeared. The voltage of the QRS complexes usually remained slightly less than that before I^{131} therapy, and T waves continued to be somewhat flatter. The decrease of the QT interval per-

The size of the heart is diminished by thyroid medication and increases if thyroid is withdrawn. Even when the cardiac silhouette appears normal on x-ray examination, a decrease in size and change in con-

figuration may be observed after the administration of thyroid.[15] Enlargement of the cardiac silhouette has been attributed to dilatation of the heart,[2] myxedematous infiltration of the myocardium[16] and, in some cases, pericardial effusion.[17]

When spontaneous myxedema is found in patients with chronic cardiovascular disease it is difficult to evaluate the influence of the metabolic disorder on heart size. Thus, in some patients with arteriosclerotic heart disease and hypothyroidism, there may be no modification in cardiac size after thyroid medication, despite an increase in the force and amplitude of cardiac contractions, increase in cardiac minute volume output and velocity of blood flow, and reversal of electrocardiographic changes.[15] In others, increase in cardiac size during thyroid therapy may be observed and is associated with a progression of the underlying cardiac disease.

In an earlier study of the x-ray changes of the heart in artificial myxedema, half a month to nine months after total thyroidectomy, an increase in heart size was noted in 15 of 22 patients (68 per cent) with congestive heart failure and 8 of 17 patients (47 per cent) with angina pectoris.[9] In spite of these changes, clinical improvement in the signs and symptoms of congestive heart failure or of angina pectoris persisted for three to twelve months.

In the present group of patients, films taken during two to fifty-three months of I^{131}-induced hypometabolism were compared with films obtained before treatment. All patients were clearly hypometabolic, and many experienced minor symptoms of hypothyroidism on 6 to 90 mg. of thyroid. Opportunity was thus afforded to study the long-term effects of controlled induced hypothyroidism in patients whose clinical progress had been closely observed.

The change in heart size after the induction of myxedema in patients with congestive heart failure is difficult to interpret. It has been described[9] as the resultant of two opposing factors: the effect of the hypothyroid state, increasing heart size, and the restoration of circulatory compensation, decreasing heart size. In the present series of 6 patients with congestive heart failure unaccompanied by angina pectoris, no definite enlargement was observed with prolonged hypothyroidism during most of the lives of the patients. In Cases 20 and 24, despite a prolonged period of hypothyroidism, no increase in the cardiac silhouette occurred until shortly before death. Consistent with previous observations[9] was Case 20, in which striking therapeutic improvement was accompanied by a 3.1-cm. decrease in the cardiac diameter. The cardiac silhouette showed a partial return to the original heart size just before death, thirty-five months after I^{131} therapy.

It might have been anticipated that prolonged unrelieved congestive heart failure and hypothyroidism would increase cardiac size. However, Case 23 showed no clinical improvement and yet no increase in cardiac diameter during fifty-three months of I^{131}-induced hypometabolism.

In contrast, both patients who experienced noticeable relief from both severe congestive heart failure and intractable angina pectoris during I^{131}-induced hypometabolism demonstrated significant progressive increase in the size of the heart shadow. In 1 (Case 26) induction of myxedema was accompanied by striking remission of both angina pectoris and congestive heart failure. The patient refused to take thyroid as ordered. Progressive cardiac enlargement was noted (Fig. 3); cardiac improvement, however, was maintained. This casts considerable doubt on the existence of the "myxedema heart" if the term is defined as a condition precipitating congestive heart failure or angina pectoris.

The interpretation of changes in the cardiac silhouette in patients with angina pectoris was not complicated by a changing state of cardiac compensation. Correlation of the x-ray changes and the clinical therapeutic result in 19 patients observed during two to forty-eight months of hypometabolism revealed a difference in the response of the cardiac size between those who achieved a worthwhile result and those who experienced no benefit from I^{131}. Thus, in 10 of 13 patients in whom good to striking relief of angina pectoris occurred, there was no increase in cardiac size during two to forty-seven months of hypothyroidism. Occasionally, a single film showed a transient increase in heart size, with return to control value in the next film. An additional 2 of these 13 patients had no increase in heart size for twenty-six and thirty-eight months, the increase occurring only during an exacerbation of angina pectoris after the period of hypothyroidism. On the other hand, in 5 of 6 patients who were not benefited by I^{131} therapy there was a progressive increase in the size of the heart shadow. The mechanism for this clear difference in the response of these two groups of patients with angina pectoris to induced hypometabolism is unknown. No relation could be observed between the pretreatment severity of angina pectoris and either the clinical improvement or the change in heart size. Nor could the depth or duration of myxedema be correlated with the change. No correlation was noted between the initial size of the heart and the presence or absence of enlargement after hypothyroidism.

We have noted above a distinction in the changes in the size and configuration of the cardiac silhouette in induced myxedema, between the cases in which a worthwhile result was achieved and those in which the result was unsatisfactory. Alterations in the electrocardiographic pattern after I^{131} therapy were so variable in extent and transient in duration that no correlation could be established between the observed electrocardiographic changes and the therapeutic result attained. Our data, however,

indicate that the "myxedema heart," in the sense of a condition precipitating angina pectoris or congestive heart failure or accompanied by marked electrocardiographic and x-ray changes, does not occur in patients with prolonged, controlled I^{131}-induced hypometabolism.

Summary

Changes in the size and configuration of the cardiac silhouette in 27 patients and variations in the electrocardiogram in 28 patients with intractable angina pectoris or congestive heart failure were studied before and for two to fifty-three months after the development of I^{131}-induced myxedema. All patients were distinctly hypothyroid and were maintained at basal metabolic rates of -15 to -25 per cent on 6 to 90 mg. of desiccated thyroid daily.

Alterations in heart size and electrocardiographic pattern were correlated with the level of hypometabolism as determined by the clinical state, basal metabolic rate, serum cholesterol, thyroid I^{131} and serum protein-bound iodine.

Ten of 13 patients who achieved good to striking relief of angina pectoris exhibited no increase in cardiac size after two to forty-eight months of hypometabolism. Two others exhibited no enlargement of the heart in twenty-six and thirty-eight months of hypometabolism during which a good or excellent therapeutic result was attained; subsequently, cardiac enlargement was noted in these cases during an exacerbation of angina pectoris and congestive heart failure.

Five of 6 patients with angina pectoris not benefited by I^{131} therapy showed a progressive increase in heart size.

Six patients with chronic congestive heart failure showed no cardiac enlargement during most of nineteen to fifty-three months of hypometabolism. In 2 patients an increase in heart size was observed only shortly before death after twenty-two and thirty-one months of hypothyroidism, during which definite therapeutic improvement was experienced.

In 2 patients with both angina pectoris and congestive heart failure I^{131}-induced myxedema was followed by striking therapeutic benefit despite progressive and marked cardiac enlargement.

The development of myxedema was accompanied by a decrease in electrocardiographic voltage, flattening or inversion of T waves and a slight decrease in the QT interval. Changes in the electrocardiogram regressed after the administration of small doses of thyroid. Thereafter, despite definite hypometabolism for months or years, no further progression in the electrocardiographic pattern occurred.

The data indicate that the "myxedema heart," in the sense of a condition precipitating angina pectoris or congestive heart failure or accompanied by marked electrocardiographic and x-ray changes, does not occur in patients with prolonged, controlled I^{131}-induced hypothyroidism.

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THE CEREBRAL CIRCULATION AND METABOLISM IN ARTERIOSCLEROTIC AND HYPERTENSIVE CEREBROVASCULAR DISEASE*

With Observations on the Effects of Inhalation of Different Concentrations of Oxygen

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RECENT studies on the pathogenesis of cerebrovascular accidents have emphasized the importance of either vasomotor changes in the cerebral vessels themselves or temporary inadequacy of the systemic circulation.[1, 2] Although such functional alterations are probably significant in the causation of cerebrovascular accidents, the existence of structural changes in the cerebral vessels is generally believed to aggravate if not actually to provide the underlying basis of the vascular episode.[3, 4] In this regard it is of interest that a reduction in both cerebral blood flow[5] and oxygen uptake[6] has been found in elderly subjects even in the absence of symptoms of cerebrovascular disease. Whether patients with overt manifestations have even greater impairment in these functions has not been definitely established. Fazekas and his associates,[6] for example, found that the reduction in cerebral metabolism in elderly persons had little relation to the presence of clinical manifestations of vascular involvement; in Scheinberg's[7] report the value for cerebral oxygen uptake in patients with cerebrovascular disease and normal mental state was the same as that in young, healthy control subjects.

This report presents our observations on the cerebral blood flow and metabolism in 48 control subjects of varying ages and in 39 patients with cerebrovascular accidents or with encephalomalacia associated with arteriosclerosis and hypertension. In addition, the effects of inhalation of 50 to 100 per cent concentrations of oxygen were studied to determine the response of diseased cerebral vessels to increased oxygen tensions and to explore the therapeutic possibilities of, or contraindications to, such alterations.

MATERIAL AND METHODS

The 39 patients with cerebral vascular disease in this study were divided into two groups, depending on the duration of their cerebral manifestations. Twenty-two of them were studied within a few days of the onset of their first cerebrovascular accident. All but 1 of these 22 patients had hypertension for several years before the presenting episode, but there was no history of previous vascular involvement of the brain. Nineteen of them had acute onset of hemiplegia of varying severity, often associated with loss of consciousness, aphasia or sensory manifestations, and in 3 others convulsions, without other evidence of motor or sensory disturbances, developed. The cerebral studies were done within one to ten days of the onset of the acute symptoms, with an average of four days. Eight of the patients were stuporous at the time of the cerebral studies; 9 others showed slight or moderate degrees of confusion, and only 5 were relatively alert and rational. The ages varied from thirty-eight to seventy-four years, with an average of fifty-nine years.

The second group of 17 patients were believed to have chronic cerebrovascular disease with moderate or advanced encephalomalacia. Twelve of them had had recurrent accidents (hemiplegias, convulsions or periods of confusion), whereas 5 had shown progressive mental deterioration without overt motor or sensory manifestations. Autopsies were performed in 3 of them, and severe atherosclerosis of cerebral vessels with extensive areas of cerebral softening was found. The ages of these patients ranged from forty-six to eighty-four years, with an average of sixty-four years. Only 9 were known to have hypertension.

None of these 39 patients had evidence of congestive heart failure or azotemia at the time of the cerebral studies, but all of them showed moderate to severe arteriolar changes in the retina. There was no evidence of neurosyphilis, cerebral emboli, brain tumor or abscess as the cause of the cerebral manifestations in any of these patients. The spinal fluid of 3 patients with initial cerebrovascular accidents was grossly bloody, whereas that in the remaining patients was clear. Autopsy was performed in 2 of the 3 patients with bloody spinal fluid and showed massive intracerebral hemorrhage.

The 48 subjects used as controls were patients convalescing from a variety of acute illnesses, such as pneumonia, peptic ulcer, hepatitis and arthritis, or from surgical procedures, such as herniorrhaphy and appendectomy. They gave no evidence of

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intracranial disease, and only 9 of them had slight hypertension, with mean blood-pressure elevations varying from 110 to 132. These control subjects were divided on the basis of age into two groups approximately equal in number. Twenty-five were between twenty and forty-four years of age, with a mean age of twenty-nine years, and 23 ranged from forty-five to seventy-five, with a mean age of fifty-six years. All the control subjects, as well as the patients with cerebrovascular disease, had hemoglobin values greater than 9.5 gm. per 100 cc.

The cerebral blood flow (CBF) in these 87 persons was measured by the nitrous oxide method of Kety and Schmidt,[8] with minor modifications previously described.[9] The cerebral oxygen consumption ($CMRO_2$) was calculated from the CBF and the cerebral arteriovenous oxygen difference. The cerebrovascular resistance (CVR) was calculated from the CBF and the mean arterial pressure measured directly from the femoral artery with a damped mercury manometer. No effort was made to obtain blood from the jugular vein on the side of the cerebral lesion, since it has been shown that there is practically no difference in the cerebral blood flow or metabolism calculated from samples simultaneously obtained from the right and left internal jugular veins of these patients.[7]

The effects of inhalation of oxygen were observed in 17 patients with cerebrovascular disease. Ten of them were allowed to inhale 85 to 100 per cent oxygen and 7 were given 50 per cent oxygen—approximately the concentration administered in tents. Control observations of the cerebral circulation in these patients were performed with the subject breathing the standard gas mixture of 21 per cent oxygen, 15 per cent nitrous oxide and 64 per cent nitrogen. After this control study, the patients were given either 50 per cent or 100 per cent oxygen by face mask for a period of twenty minutes, the gas being changed to mixtures containing 15 per cent nitrous oxide with 50 per cent or 85 per cent oxygen, respectively, with the remainder nitrogen, and a second blood-flow determination carried out.

Samples of arterial and venous blood drawn just before and at the end of each blood-flow procedure were pooled, and their oxygen and carbon dioxide content was measured by the combined procedure described by Peters and Van Slyke.[10] The nitrous oxide content of blood samples was determined by the manometric method of Orcutt and Waters.[11] Modifications of these gasometric technics, suggested by Kety and Schmidt,[8] were employed. Early in the study we determined the oxygen capacity of blood by equilibrating the sample with air in a small flask, analyzing for oxygen manometrically and making the usual correction for dissolved oxygen. More recently the method of Roughton and his associates[12] was employed. Hemoglobin concentration was calculated from the oxygen capacity. Arterial pH was measured with the glass electrode of a Cambridge Model R pH meter and corrected to body temperature.[13] Arterial carbon dioxide tension (pCO_2) was calculated from the pH, carbon dioxide content and hematocrit by means of the nomogram of Singer and Hastings.[14] Arterial oxygen tension (pO_2) was calculated from the pH and the per cent oxyhemoglobin saturation by means of the dissociation curves of Dill.[15]

Table 1. *Mean Values for Cerebral Functions in Control Subjects and in Patients with Acute and Chronic Vascular Disease.*

Group	Mean Age	Cerebral Blood Flow	Cerebral Oxygen Consumption	Cerebral Vascular Resistance	Arteriovenous Oxygen Difference	Mean Arterial Blood Pressure
	yr.	*cc./100 gm./min.*	*cc./100 gm./min.*	*mm.Hg./cc./100 gm./min.*	*vol. per cent*	
Control subjects:						
Under 45 yr. of age	29	52	3.1	1.8	6.1	91
Over 45 yr. of age	56	46*	2.9	2.2*	6.3	101
Patients with vascular disease:						
Acute	59	40†	2.7*	3.1†	6.9*	120
Chronic	64	35†	2.1†	3.3†	6.1	114

*Indicates statistically significant differences ($p < 0.05$) from mean values of control subjects less than 45 yr. of age.

†Indicates statistically significant differences ($p < 0.01$) from mean values of both groups of control subjects.

Results

The mean CBF in the 25 control subjects less than forty-five years of age was 52 cc. per 100 gm. of brain per minute, which is somewhat greater ($0.05 > p > 0.02$) than the value of 46 cc. observed in the group of older controls (Table 1 and Fig. 1). Both the patients with initial acute cerebrovascular accidents and those with recurrent or chronic manifestations, however, had statistically significant reductions in the mean CBF with values of 40 and 35 cc., respectively. Only 4 of the total group of 39 patients with vascular disease showed values greater than the mean values observed in the control subjects. Although the average age of the older group of control subjects was somewhat less than those of the two groups of patients with vascular disease, the differences in age did not account for the differences in CBF, since the 13 control subjects

over fifty (average age of sixty-three years) had the same CBF value as the entire group of subjects over forty-five years of age.

The $CMRO_2$ in the younger group of control subjects averaged 3.1 cc. per 100 gm. of brain per minute (Fig. 2), whereas those over forty-five years showed a slight reduction in the cerebral metabolic rate, with a mean value of 2.9 cc. ($0.1 > p > 0.05$). The mean $CMRO_2$ in the patients with an acute cerebrovascular accident was 2.7 cc., a value only slightly less than that observed in either group of control subjects. There was, however, a marked reduction in the cerebral metabolic rate in the 17 patients with symptoms of chronic progressive cerebrovascular disease. These patients had a mean $CMRO_2$ of 2.1 cc., which is significantly less ($p < 0.01$) than that observed in each of the other three groups of patients. Only one of the patients with chronic cerebrovascular manifestations had a $CMRO_2$ value greater than the mean value of the control subjects. The major changes in the $CMRO_2$ as calculated were due to reductions in cerebral blood flow of the various groups of subjects and not to decreases in arteriovenous oxygen differences.

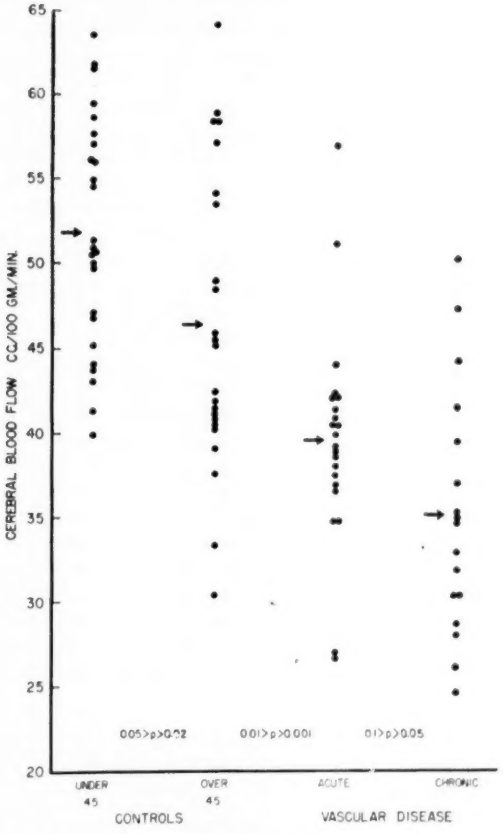

FIGURE 1. *Values for Cerebral Blood Flow in Individual Control Subjects and Patients with Cerebrovascular Accidents. The arrows indicate the mean CBF in each group. The p values represent significance of difference of mean values of patients in adjacent columns.*

In the patients with acute cerebrovascular disease, little correlation was found between the mental state of the patient at the time of the study and the cerebral oxygen consumption (Fig. 3). The mean values for $CMRO_2$ in this group was practically the same, regardless of whether they were alert, confused or stuporous. Actually, 1 patient, completely stuporous as a result of intracerebral hemorrhage, had a $CMRO_2$ value greater than normal.

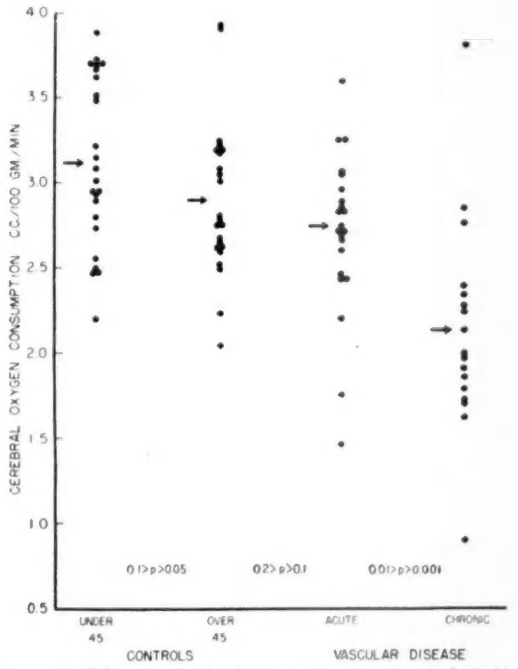

FIGURE 2. *Values for Cerebral Oxygen Consumption in Individual Control Subjects and Patients with Cerebrovascular Accidents. The arrows indicate the mean $CMRO_2$ in each group. The p values represent significance of difference of mean values of patients in adjacent columns.*

Cerebral studies were repeated within five weeks of the initial studies in 6 patients with a single cerebrovascular accident and 2 of those with recurrent manifestations (Table 2). There was a slight increase in the mean CBF from 36 to 41 cc. in these 8 patients, a slight decrease in CVR, but no change in the mean $CMRO_2$. Five of the 6 patients with initial cerebrovascular accidents showed an increase in CBF at the time of the second study.

The administration of 85 to 100 per cent oxygen resulted in a definite reduction in CBF in 7 of 10 patients with cerebrovascular disease (Table 3

and Fig. 4). This concentration of oxygen produced a 9 per cent decrease in mean CBF flow and a 13 per cent increase in mean CVR. These changes are comparable to those observed in control subjects,

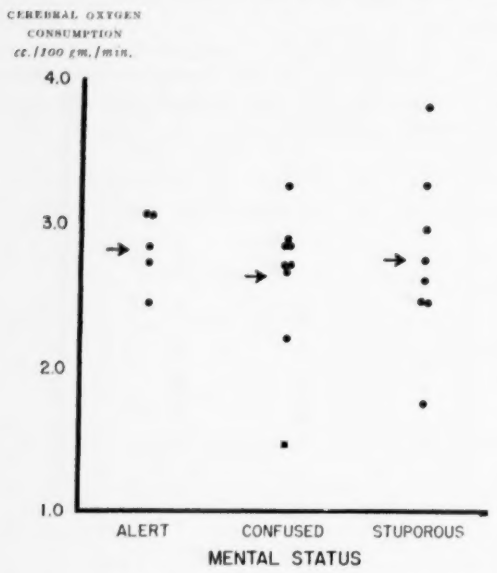

FIGURE 3. *Values for Cerebral Oxygen Consumption in Individual Patients with Initial Cerebrovascular Accidents. The arrows indicate mean values in each group.*

in whom a 14 per cent reduction in the mean CBF and a 15 per cent increase in mean CVR occurred. There was no significant change in cerebral metabolism in either the control patients or those with

of the patients gave any evidence of clinical improvement in hemiplegia or mental state during inhalation of oxygen. On the contrary, 1 showed mental confusion, a fall in blood pressure and a transient hemiplegia five minutes after cessation of oxygen inhalation; the CBF fell from 40 to 34 cc., and the $CMRO_2$ from 3.1 to 2.7 cc. per 100 gm. of brain per minute.

DISCUSSION

The reduction in CBF and the elevation of CVR found in the control subjects over forty-five years of age was, in all probability, caused by a moderate degree of arteriosclerosis insufficient to alter cerebral function to the point of overt manifestations. Beginning in about the fourth decade numerous alterations have been observed in all the layers of the cerebral arteries.[16] These changes become more extensive during the fifth and sixth decades and may account for the abnormal values in CBF and CVR noted in the older control subjects. Although 9 of these patients had an elevation in blood pressure, with a mean arterial pressure of 110 or more, this finding alone has not been found to be associated with a decrease in CBF.[17] The more marked reduction in CBF noted after a single cerebrovascular accident was most probably due to diffuse atherosclerosis throughout most of the cerebral vessels, even though these patients had previously been in good health. This situation is analogous in some respects to that observed in patients with coronary-artery disease, in whom considerable narrowing of one or more coronary vessels may exist without causing clinical signs or symptoms of cardiovascular disease.[18] It is also possible that the patients with acute cerebrovascular accidents

TABLE 2. *Changes in Cerebral Function of 8 Patients with Acute and Chronic Cerebrovascular Disease.*

PATIENT	SYMPTOMS	PERIOD AFTER VASCULAR ACCIDENT		MENTAL STATUS		CBF	
		INITIAL STUDY *days*	FOLLOW-UP STUDY *days*	INITIAL STUDY	FOLLOW-UP STUDY	INITIAL STUDY *cc./100 gm./min.*	FOLLOW-UP STUDY *cc./100 gm./min.*
G. P.*	Convulsions; coma.	1	8	Stuporous	Alert	44	51
T. C.*	Horner's syndrome; hemianesthesia.	9	20	Stuporous	No change	29	25
L. T.	Convulsions	3	35	Confused	Alert	41	26
W. F.	Convulsions; stupor.	2	31	Stuporous	Slightly confused	39	57
B. S.	Aphasia; right hemiplegia.	4	12	Lethargic	Alert	27	48
L. S.	Right hemiplegia	4	16	Confused	Lethargic	35	39
J. M.	Aphasia; right hemiplegia.	1	3	Lethargic	Slightly confused	42	51
B. J.	Right hemiplegia; coma.	1	11	Comatose	Stuporous	27	35
Mean values						36	41

*Patient with recurrent cerebrovascular manifestations.

cerebrovascular accidents. Inhalation of 50 per cent oxygen tended to cause the same alterations in cerebral functions as higher concentrations of the gas, but the changes were not as marked. None

had a superimposed functional abnormality in the form of reflex vasoconstriction at the time of the accident. The definite increase in blood flow, observed within a month of the onset of the acute

manifestations in 5 of the patients with initial cerebrovascular accidents, lends support to this hypothesis.

The slight decrease in cerebral oxygen uptake noted in the control subjects over forty-five years of age is at variance with the pronounced reduction in cerebral metabolism observed by Fazekas and his associates[6] in a comparable, but slightly older, group of subjects. The $CMRO_2$ in our patients with a single acute vascular accident was only slightly less than that found in control patients over forty-five years of age. It seems likely that, although these patients had only one overt cerebrovascular accident, some of them had a moderate degree of pre-existing encephalomalacia. Indeed, 2 of them had $CMRO_2$ values less than 2 cc. and, in this respect, were comparable to the majority of those with recurrent vascular episodes. In general, the patients with recurrent episodes of cerebrovascular accidents had a greater reduction in both blood flow and metabolism than those with only a single accident. In many respects both the clinical manifestations and the abnormalities in cerebral functions of the patients with mental deterioration caused by arteriosclerosis resembled those seen in paretic neurosyphilis.[9]

It should be pointed out that the CBF, as measured by the nitrous oxide method, represents chiefly the flow through *perfused* brain. If areas of the brain are devoid of blood supply or so poorly perfused that nitrous oxide equilibrium is not established by the end of the flow procedure, the actual blood flow per unit weight of brain may be lower than that indicated in this study. Furthermore, since some of the patients probably had a moderate degree of cerebral atrophy, the total blood flow through the brain of these patients may have been reduced to an even greater extent. A reduction in the total intracranial blood flow, as measured by the rate of spinal-fluid displacement, has been reported in patients with cerebral atrophy associated with cerebral arteriosclerosis.[19]

In the patients with initial cerebrovascular accidents, no correlation was observed between the cerebral metabolic rate and the degree of confusion or stupor at the time of the blood flow. On the other hand, there was a definite tendency in the patients with progressive mental deterioration and other evidence of encephalomalacia to show a considerable reduction in CBF and metabolism. Similar observations have been made by Scheinberg,[7] who noted a marked reduction in both CBF and $CMRO_2$ in patients with cerebrovascular disease and mental changes.

The fact that inhalation of oxygen failed to increase the cerebral oxygen uptake of these patients is of interest, since patients with strokes are often given oxygen therapy. The question of the therapeutic value of 100 per cent oxygen arises in these patients. There can be no doubt that oxygen therapy is indicated in patients with cerebrovascular accidents who have decreased arterial oxygen saturation because of pulmonary edema or other types of pulmonary disturbance. Even in patients with normal oxygen saturation of the arterial blood, the administration of 85 to 100 per cent oxygen produced a marked increase in arterial oxygen tension and an increase in oxygen content of 1.7 cc. per 100 cc. of blood. In experimental myocardial infarction, such changes provide a considerable increase in oxygen tension in the tissues adjacent to the central necrotic area,[20] and a similar situation may obtain in cerebral infarction.

The inhalation of 85 to 100 per cent oxygen produced a decrease in the mean CBF that largely offset the increase in arterial oxygen content. Thus, there was no significant alteration in the oxygen delivery to the brain in our patients, as calculated from the product of the CBF and the arterial oxygen

TABLE 2 (*Concluded*).

PATIENT	$CMRO_2$		CVR		REMARKS
	INITIAL STUDY	FOLLOW-UP STUDY	INITIAL STUDY	FOLLOW-UP STUDY	
	cc./100 gm./min.	*cc./100 gm./min.*	*mm. Hg./cc./100 gm./min.*	*mm. Hg./cc./100 gm./min.*	
G. P.	2.2	3.5	3.0	2.8	Hemiplegia, 4 mo. previously; convulsions, 1 wk. previously.
T. C.	1.8	1.2	3.5	4.1	Mental changes, 1 yr.; acute cerebellar-artery syndrome.
L. T.	2.9	1.2	3.7	6.7	Hypertensive encephalopathy; no motor weaknesses.
W. F.	2.5	2.7	4.2	3.1	Hypertensive encephalopathy; no motor weaknesses.
B. S.	1.5	2.7	5.1	2.5	Patient hypertensive; motor strength improved at second study.
L. S.	2.2	2.1	3.2	3.2	Patient hypertensive; spinal-fluid pleocytosis improved at second study.
J. M.	3.3	3.1	2.2	1.7	Patient hypertensive; motor weakness improved at second study.
B. J.	2.6	2.5	5.7	3.1	Intracerebral hemorrhage; patient died 2 days after second study.
Mean values	2.4	2.4	3.8	3.4	

content (Table 3). It is theoretically possible that the decrease in the caliber of the cerebral vessels produced by 100 per cent oxygen would increase stasis sufficiently to precipitate thrombosis in vessels cause a reduction in the cerebral glucose delivery. This factor may sometimes be of consequence, particularly in the presence of a low blood sugar, since progressive reductions of blood glucose are associated

TABLE 3. *Mean Values for Cerebral Functions before and during Administration of 50 to 100 Per Cent Oxygen.*

SUBJECT	CONCENTRATION OF OXYGEN	NO. OF PATIENTS	MEAN AGE	CBF		$CMRO_2$		CVR	
				AIR	OXYGEN	AIR	OXYGEN	AIR	OXYGEN
	%		yr.	cc./100 gm./min.	cc./100 gm./min.	cc./100 gm./min.	cc./100 gm./min.	mm. Hg./cc./100 gm./min.	mm. Hg./cc./100 gm./min.
Control	50	8	31	47	43	3.4	3.2	1.9	2.1
	85–100	10	31	49	43	2.9	3.1	1.9	2.1
Patients with cerebrovascular accident	50	7*	65	37	35	2.9	2.9	3.4	3.5
	85–100	10†	63	36	33	2.3	2.4	2.8	3.2

TABLE 3 (*Concluded*).

MEAN ARTERIAL PRESSURE		ARTERIOVENOUS OXYGEN DIFFERENCE		VENOUS OXYGEN TENSION		ARTERIAL OXYGEN CONTENT		CEREBRAL OXYGEN DELIVERY	
AIR	OXYGEN	AIR	OXYGEN	AIR	OXYGEN	AIR	OXYGEN	AIR	OXYGEN
mm. Hg.	mm. Hg.	vol. per cent	vol. per cent	mm. Hg.	mm. Hg.	vol. per cent	vol. per cent	cc./100 gm./min.	cc./100 gm./min.
86	89	7.4	7.6	28	31	15.8	16.6	7.1	6.8
93	91	5.9	7.1	31‡	31‡	15.9	17.6	7.9	7.7
115	116	8.0	8.2	27	30	17.2	18.2	6.2	6.4
105	105	6.4	7.4	30‡	34‡	16.1	18.4	5.9	6.1

*Includes 5 patients with acute and 2 with chronic vascular disease.
†Includes 6 patients with acute and 4 with chronic vascular disease.
‡Data calculated from an assumed pH of 7.35.

in which the flow was already critically reduced. The administration of 100 per cent oxygen is known to reduce coronary blood flow and in patients with

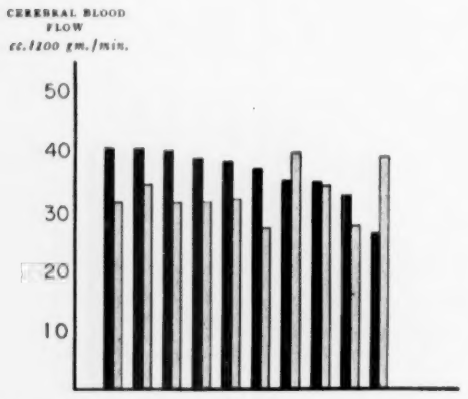

FIGURE 4. *Effects of Inhalation of High Concentrations of Oxygen on the Cerebral Blood Flow in Patients with Cerebrovascular Accidents.*

The solid columns represent determinations during inhalation of 21 per cent and the stippled columns determinations during inhalation of 85 to 100 per cent oxygen.

angina pectoris produces more pronounced and persistent electrocardiographic alterations after standard exercise.[21] It should also be borne in mind that a decrease in CBF during oxygen therapy may with measurable decreases in cerebral oxygen uptake.[22] In view of these considerations, it may be wiser to avoid administration of 100 per cent oxygen by mask in patients with cerebrovascular disease and to employ concentrations of approximately 35 to 50 per cent, such as that given by nasal catheter or tent. Such concentrations have only slight vasoconstrictive effect on cerebral vessels and produce a small increase in venous oxygen tension, and probably in cerebral-tissue oxygen tension as well. Whether such increases in oxygen tension are sufficient to maintain cellular viability in areas that would otherwise be incorporated in the infarct is a matter for further study.

SUMMARY

The cerebral blood flow (CBF), cerebral oxygen consumption ($CMRO_2$) and cerebrovascular resistance (CVR) were determined by the nitrous oxide technic in 48 control subjects of varying ages and in 39 patients with cerebrovascular accidents or with encephalomalacia caused by arteriosclerosis and hypertension. The effects of inhalation of 50 to 100 per cent concentrations of oxygen were studied in some of these cases.

The mean CBF in a group of older control subjects was somewhat less than that found in young, healthy subjects, and patients with cerebrovascular accidents showed even greater reductions in blood flow values. The $CMRO_2$ of older control subjects was only slightly less than that of young, healthy

persons. A marked reduction of cerebral oxygen consumption was found in patients with chronic cerebrovascular disease.

The administration of 85 to 100 per cent oxygen to patients with cerebrovascular accidents caused a reduction of cerebral blood flow, whereas 50 per cent oxygen produced little change in this function. The oxygen uptake of the brain was unaffected by either concentration.

The reduction in cerebral blood flow found in control subjects over forty-five years of age and in patients with cerebrovascular accidents suggests that arteriosclerotic changes exist throughout most of the cerebral vessels of such persons. In view of the vasoconstrictive effect of inhalation of 100 per cent oxygen it may be wiser to avoid the use of this concentration of gas in patients with cerebrovascular accidents.

We are indebted to Misses Mary Bell, Mary Fordham, Mary Upshaw and Mrs. Louise Thompson for their technical assistance.

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NOR-EPINEPHRINE IN THE TREATMENT OF ACUTE MENINGOCOCCEMIA WITH SHOCK (WATERHOUSE-FRIDERICHSEN SYNDROME) AND AN EVALUATION OF ADRENOCORTICAL FUNCTION*

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BEFORE the advent of the sulfonamides, recovery from the Waterhouse–Friderichsen syndrome was rare.[1] Thereafter, isolated case reports described successful treatment of this fulminating infection, and by 1948 Brand[2] reviewed 25 cases with recovery and added 1 of his own. When penicillin and the sulfonamides were combined, the results in all types of meningococcal infections improved greatly[3-9]; however, many patients with the Waterhouse–Friderichsen syndrome continued to die in shock, despite the liberal use of antibiotic and chemotherapeutic agents. Vigorous adrenal substitution therapy, including parenteral administration of epinephrine, has been advocated by Thorn and his associates,[10] and recently there have been reports of the successful use of cortisone.[1, 11] However, treatment of the peripheral vascular collapse during the first twenty-four to forty-eight hours remains the major therapeutic problem. Two comprehensive reports have described excellent results with nor-epinephrine in the treatment of peripheral vascular collapse from such causes as myocardial infarction, sepsis, postoperative shock, acute surgical emergencies and anesthetic complications.[12, 13]

This report describes a classic case of the Waterhouse–Friderichsen syndrome in which the intravenous infusion of nor-epinephrine was carried out during the first sixty hours to combat circulatory collapse and maintain a normal blood pressure.

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Case Report

K. F., a 17-year-old boy, was admitted in a condition of acute illness and prostration to the City of Detroit Receiving Hospital on January 26, 1952. Two weeks before admission he had contracted a mild respiratory infection, from which he had com-

pletely recovered within a few days, except for persistence of malaise, anorexia and a mild sore throat. On the night before admission, he noticed a "stiff neck," and suffered a severe chill with intense occipital headache; although he took symptomatic therapy, he was restless and uncomfortable throughout the night. In the morning, when vomiting and diarrhea developed, he collapsed on the floor.

Physical examination revealed a well developed and well nourished, but acutely ill, prostrate boy. There was a cyanotic tinge to the lips and the nail beds. Petechiae were scattered over the entire body surface and in the conjunctival and buccal mucosas. Funduscopic examination showed hyperemia of the retina. The neck was supple, and there was no cervical lymphadenopathy. The lungs were clear to percussion and auscultation, and the heart sounds were rapid and of poor and distant quality. The abdomen was flat and soft, and no organs or masses were palpable. No abnormalities of the genitalia were noted, and

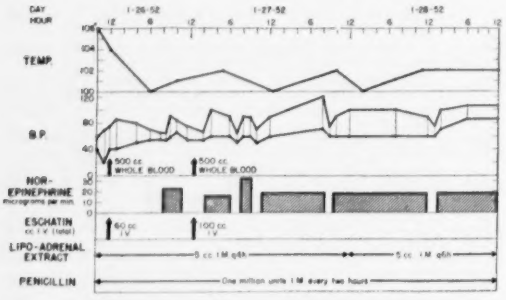

FIGURE 1. *Course of the Patient's Illness in Relation to Nor-epinephrine and Other Therapy during the First Three Hospital Days.*

rectal examination was negative. Neurologic examination demonstrated no localizing signs.

The temperature was 106.2°F., by rectum, the pulse 130, and the respirations 18. The blood pressure was at first unobtainable, but rose to 60/40 after intravenous infusions of fluids were started.

Examination of the blood disclosed a hemoglobin of 16 gm. per 100 cc., and a white-cell count of 20,800, with 91 per cent neutrophils, 8 per cent lymphocytes and 1 per cent monocytes. Urinalysis showed a ++++ test for albumin, and a negative test for sugar, with 7 to 10 white blood cells and 1 to 3 red blood cells per high-power field in the sediment. The cerebrospinal fluid was clear and colorless, with 3 white blood cells and 6 red blood cells per cubic millimeter. The sugar was 122 mg. and the protein 28 mg. per 100 cc., and the chloride 113 milliequiv. per liter. The spinal-fluid smear was negative, and culture failed to grow any organisms. Blood was drawn for culture before any therapy was instituted and was reported on the 4th hospital day as positive for *Neisseria meningitidis*. Initial blood chemical values were as follows: blood sugar 80 mg., and blood urea nitrogen 12 mg. per 100 cc., and plasma chloride 100 milliequiv. per liter.

Vigorous therapy was instituted immediately, including nasal administration of oxygen, an intravenous infusion of 5 gm. of sodium sulfadiazine in 1 liter of physiologic saline solution with 1,000,000 units of crystalline penicillin and 5 cc. of aqueous adrenocortical extract added. In addition, 5 cc. of Lipo-adrenal Extract and another 5 cc. of the aqueous extract were given intramuscularly. The patient then received 50 cc. of the aqueous extract intravenously. A transfusion of 500 cc. of whole blood followed the 1st liter of physiologic saline solution.

The course of the illness from the time of admission is shown in Figure 1. After the initial rise in the blood pressure that occurred within the 1st 3 hours, there was a slow but steady fall, with a marked narrowing of the pulse pressure. At that time the patient had received 60 cc. of aqueous adrenocortical extract parenterally, 500 cc. of blood and several liters of glucose and glucose-saline solution. Nine and a half hours after admission it was clear that all therapy to combat the development of irreversible shock was failing. At this point, an intravenous infusion of nor-epinephrine in a concentration of 4 mg. per liter of 5 per cent glucose solution was instituted at a rate of 23 microgm. per minute.

The blood pressure rose sharply soon after initiation of nor-epinephrine and was maintained at low normal levels during the 2-hour course of the 1st infusion, but fell to shock levels shortly after discontinuation (Fig. 1). A 2d attempt to support blood pressure with 100 cc. of aqueous adrenocortical extract and a blood transfusion was unsuccessful; subsequent reinstitution of nor-epinephrine produced a prompt rise that was sustained as long as the infusion was continued. Figure 1 demonstrates clearly the relation of blood-pressure levels to the nor-epinephrine therapy. The rate of infusion varied from 17 to 33 microgm. per minute at first, but later a stable blood-pressure level was attained at a constant flow of 19 microgm. per minute.

On the 2d hospital day, the white-cell count had risen to 37,650; the urine gave a + test for albumin, and the sediment contained about 100 white blood cells and over 200 red blood cells per high-power field, together with many granular casts. On the 4th day a complete hematologic study showed a red-cell count of 6,000,000, with a hemoglobin of 15 gm. per 100 cc., and a white-cell count of 20,300, with 95 per cent neutrophils; there were 206,000 platelets and a total eosinophil count of 91 per cubic millimeter. Bleeding and clotting times were ½ minute and 16 minutes, respectively. The urine was clear, with only a trace of albumin. At this time, since the patient had successfully passed the critical phase of his illness, the various therapeutic agents were gradually reduced and then discontinued, with the exception of penicillin, which was administered until the week before discharge.

In an attempt to evaluate adrenocortical function, eosinophil counts and 17-ketosteroid excretion levels were determined within 72 hours of admission. Two days before discharge, when the patient was clinically well, a 48-hour ACTH test was made and these responses were re-evaluated. Seventy-two hours after admission the initial eosinophil count was 91 per cubic millimeter; 2 days later the count was 225 per cubic millimeter. On the 3d hospital day the 17-ketosteroid excretion was 20.4 mg. per 24 hours. Before the ACTH test, analysis of a control urine specimen showed a steroid excretion rate of 12.3 mg. per 24 hours. Twenty milligrams of ACTH was then given intramuscularly in the morning, and thereafter 10 mg. was given intramuscularly every 6 hours for 48 hours. The total circulating eosinophil count at the end of 24 and 48 hours was 244 and 394, respectively. At 24 hours the 17-ketosteroid excretion was only 13.6 mg. per 24 hours; at 48 hours, however, it was 21.9 mg. per 24 hours. A final evaluation of the response of the eosinophil count was made in the Out Patient Department 3 weeks later, and there was a prompt fall from 632 to 277 per cubic millimeter 4 hours after the subcutaneous administration of 0.5 cc. of epinephrine.

DISCUSSION

After the diagnosis of Waterhouse–Friderichsen syndrome has been made, the primary problem today is to combat the peripheral vascular collapse that is often fatal in the early hours of the illness. Successful therapy of this overwhelming infection and bacteremia, therefore, lies in the generous use of antibacterial agents combined with vigorous steps to raise the blood pressure to a normal level.

The pathogenesis of the peripheral vascular collapse remains obscure. Lesions of the central nervous system are not essential, as illustrated by the case reported above and as demonstrated by Daniels,[9] who reviewed 156 fatal cases of Waterhouse–Friderichsen syndrome of meningococcal origin. About half the patients in this series had no meningitis, about a third had mild meningitis, and a sixth had moderate to severe meningitis. Thus, meningitis is not an important etiologic factor in the shock associated with meningococcal infections.

Acute adrenal insufficiency, on the other hand, has long been considered a significant element in the syndrome. In Daniels' study, analysis of the adrenal glands at autopsy revealed a rough inverse correlation between the duration of life and the degree of frank adrenal hemorrhage. Almost half the patients had severe adrenal hemorrhages, with an average life span of sixteen hours, whereas those with mild hemorrhages lived about forty-eight hours. The inference from this analysis is that the primary cause of shock in Waterhouse–Friderichsen syndrome is adrenal hemorrhage with acute adrenal insufficiency. However, Ferguson and Chapman[14] stated that there is often insufficient adrenal damage to explain the collapse. In analyzing the autopsies of 16 cases of acute meningococcemia, they found 9 cases of gross adrenal hemorrhage with edema. In 15 of 16 cases, microscopical examination revealed pathologic changes including focal hemorrhages; focal necrosis, usually in the medulla; "tubular" degeneration of Rich in a few with hemorrhage; thrombosis of the capillaries between the medulla and cortex; and 2 cases with questionable infarctions. The authors believed that this adrenal lesion was insufficient to explain the irreversible shock and concluded that the ultimate cause of peripheral vascular collapse was extensive vascular damage with capillary hyaline thrombosis, which they found throughout the body, including the skin.

In the case reported above, the vascular collapse did not appear to be entirely the result of adrenocortical insufficiency. Evaluation of adrenocortical function by eosinophil counts and analysis of 17-ketosteroid excretion revealed no evidence of adrenal insufficiency. It may be argued that the use of Lipo-adrenal Extract contributed directly to the elevated 17-ketosteroid excretion level or that nor-epinephrine contributed indirectly by stimulating the release of pituitary ACTH; however, there was no rise in the 17-ketosteroid excretion level of a young female patient with acute meningococcal bacteremia who received both Lipo-adrenal Extract and nor-epinephrine infusion. The low initial eosinophil count was probably secondary to stimulation of the pituitary-adrenal axis by the acute infection, although the use of Lipo-adrenal Extract may have contributed. Furthermore, it has been demonstrated that nor-epinephrine produces no significant decrease in circulating eosinophils.[15] The failure of the eosinophil level to fall during the forty-eight-hour ACTH test performed after the patient had recovered from his illness is a phenomenon previously observed in patients recently convalescent from a severe infectious disease, and is attributed to a refractory recovery state of no pathologic significance. Later, there was a normal response to the four-hour epinephrine eosinophil test.

Although the primary etiologic factor in the Waterhouse–Friderichsen syndrome remains an unsolved problem, indirect evidence that it is not acute adrenocortical insufficiency can be drawn from the fact that adrenocortical substitution therapy frequently does not prevent death. For example, the use of adrenocortical extract and DOCA usually fails to reverse the shock. On the other hand, the final evaluation of cortisone, recently successful in isolated cases, has yet to be made, and the effectiveness of intravenous Compound F remains to be described.

In these studies, the prompt reversal of peripheral vascular collapse with the institution of nor-epinephrine therapy and the failure of adrenocortical substitution therapy to prevent shock strongly suggest that the Waterhouse–Friderichsen syndrome is not secondary to acute adrenocortical insufficiency. There was probably no serious impairment of the tested adrenocortical function during the acute phase of the illness in the case reported above.

I believe that the use of a continuous infusion of nor-epinephrine to maintain a normal blood-pressure level in this patient was probably a life-saving measure and prevented irreversible shock and serious renal damage from prolonged ischemia. It is suggested that the use of this vasopressor agent be considered in all cases of septicemia with peripheral vascular collapse, especially when adequate trial with blood transfusions, plasma, fluids and adrenal substitution therapy has been unsuccessful in forestalling shock.

Summary

A classic case of the Waterhouse–Friderichsen syndrome in which an intravenous infusion of nor-epinephrine was used successfully over a period of sixty hours to combat peripheral vascular collapse is described in detail. Physiologic studies of adrenocortical function during the acute stage of the illness and after recovery indicated no failure of the adrenal cortex, even in the presence of shock, which responded to nor-epinephrine but not to parenteral adrenocortical replacement therapy. The significance of these findings in relation to the pathogenesis of peripheral vascular collapse in this syndrome is discussed.

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MEDICINE'S NUMBER ONE PROBLEM*

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IMPROVEMENT in the health of the people in the developed parts of the world since 1900 constitutes one of the great achievements of the past half-century. It has been estimated, from fossil endings, that in prehistoric times the average man lived about eighteen years, his life frequently terminating in violent death. This had advanced to around twenty-five during the time of the ancient Romans. However, in 1940 in the United States, the average person could expect to live to be sixty-two, in Sweden to sixty-seven, in Canada to sixty-four, in Finland to fifty-eight, in the Netherlands to sixty-six, and in Denmark to sixty-six. The expectancy has further increased within the past ten years, reaching sixty-eight in the United States in 1949.

Although some nations of the world still have pressing problems of communicable disease and life expectancy rates vary from nation to nation, the trend in all nations is to a greatly increased life expectancy — resulting throughout the world, in an aging population. As a result, the foremost medical problem in many parts of the world is no longer the acute communicable diseases, which claimed their victims with dramatic swiftness, but the slow, insidious processes of the chronic diseases and the disabilities that they leave in their wake.

The problems to be faced extend far beyond any one discipline, agency or group; they must be solved by the community as a whole — but they can be solved only with responsible medical leadership.

One of the most significant developments in rehabilitation during the past decade has been the increasing interest, both professional and public, in the development of rehabilitation centers, and the recognition given medical rehabilitation as an integral part of medical care. Just as satisfactory job placement is the capstone of any successful program of services to the handicapped, medical rehabilitation, starting at the earliest possible moment after acute illness or injury, is the foundation, since all subsequent rehabilitation processes are built upon the residual physical disability that medical care cannot eliminate.

Until recent years the great majority of the medical profession looked upon rehabilitation as an extracurricular activity, something dealing with social work and vocational training, but something that had little concern or held but few implications for medicine. Today, however, that trend is being reversed, and although there are still many physicians who are unfamiliar with the aims and procedures of rehabilitation, medicine is beginning to recognize more and more, that medical care cannot be considered complete until the patient with a residual physical disability has been trained to live and work with what he has left.

Lacking specific measures in the care of many of the chronic diseases, medicine must look to rehabilitation to teach those afflicted by disability to live and to work as effectively as possible. Until the specific answers to the problems of diseases of the heart and circulation, rheumatic fever, arthritis, cerebral palsy, multiple sclerosis, poliomyelitis and the other crippling diseases have been found, one must utilize the technics of physical rehabilitation, psychology, social service, vocational counseling and the auxiliary specialties to teach the disabled to live within the limits of their disabilities but to the full extent of their capacities.

Although excellent hospitals, public-health centers and other facilities for preventive and definitive medicine are available in various parts of the world, there are, in comparison, but a handful of facilities equipped to provide for the patient with a physical disability the necessary retraining in physical skills that are essential for later vocational training. In the past, the physician has thought too much about the physiologic and clinical aspects of the patient's disability. The vocational counselor too frequently has thought only in terms of physical skills that could be utilized vocationally. Between the two, however, there is a wide area

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through which most physically handicapped persons must go when their medical care is completed but before they are ready to undergo vocational training. In this area lies the physical retraining in skills necessary for the carrying on of the activities inherent in daily living and common to all types of work.

Except in a few cases, the physically handicapped person must be retrained to walk and travel, to care for his daily needs, to use normal methods of transportation, to use ordinary toilet facilities, to apply and remove his own prosthetic devices and to communicate either orally or in writing. These are such simple things that they are frequently overlooked, but the personal, vocational and social success of the handicapped person is dependent upon them.

The practice of rehabilitation for the general practitioner, or for any doctor, begins with the belief in the basic philosophy that the doctor's responsibility does not end when the acute illness has ended or surgery has been completed; it ends only when the patient has been retrained to live and to work with what is left. This basic concept of the doctor's responsibility can be achieved only if rehabilitation is considered an integral part of medical service. Any program of rehabilitation is only as sound as the basic medical service of which it is a part. The diagnosis and prognosis must be accurate, for it is upon them that the feasibility of retraining is determined.

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MEDICAL PROGRESS

MEDICAL MANAGEMENT OF PERIPHERAL ARTERIAL OCCLUSIVE DISEASES*

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THE treatment of the patient with peripheral arterial insufficiency is increasingly successful. During the course of the disease, however, the physician is frequently called upon to resolve problems about which there is diversity of opinion. These include the significance of vascular calcification, the value of arteriography, the hazards of nicotine, the role of anticoagulant and antispasmodic drugs, the treatment of intermittent claudication, the therapy of acute arterial obstruction and the prophylaxis and management of impending or frank ulceration and gangrene. Finally, opinions differ concerning the indications for sympathectomy, embolectomy, segmental arterial resection and amputation. It is the aim of this paper to review the pathologic physiology of peripheral arterial insufficiency and to re-examine some of the diagnostic and therapeutic measures that have been proposed for its effective clinical management.

PATHOLOGIC PHYSIOLOGY OF ARTERIAL INSUFFICIENCY

Arterial Obstruction

Many diseases may affect the peripheral arteries and encroach upon their lumens. Thromboembolic obstruction, thromboangiitis obliterans, polyarteritis nodosa, scleroderma and the arteritis associated with systemic infection may be encountered. These conditions are responsible for a definite but small percentage of clinically recognized peripheral arterial occlusive disease. Atheromatosis, leading to narrowing and complete obliteration of the arterial lumen, is the most frequent cause of arterial insufficiency in the lower extremity. The disturbance in function, however, is primarily dependent upon the location, extent and rate of development of the arterial obstruction rather than its specific etiology.

Anatomic studies[1, 2] have demonstrated that atherosclerotic occlusions occur less frequently in the iliac, femoral and popliteal arteries than in the tibial vessels. It has also been shown[2] that there are relatively few occlusions in the lateral or terminal branches of the tibial arteries. These investigations have established the fact that the principal bottleneck to the flow of blood from the aorta to the toes occurs in the three main arteries of the lower leg. A new method of injecting and dissecting the arteries of amputated limbs has facilitated the quantitative determination of the extent of the occlusive process.[2] This technic has demonstrated that occlusive disease in the lower leg is extensive before amputation is necessary. Invariably, one or more complete occlusions were found in each injected specimen; in more than 90 per cent of the legs two or more of the four major arteries of the lower leg (the popliteal, anterior tibial, posterior tibial and peroneal) were occluded, usually at more than one point, with an average of eight sites of complete occlusion per leg. More than a fourth and frequently a half of the lengths of these major arteries were occluded by the time amputation was necessary.[2]

Various studies have shown that when sudden embolic or thrombotic occlusions occur in periph-

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eral arteries, the threat to viability is greater the nearer the lesions are to the aorta.[3, 4] Thrombosis is not uncommon in patients with chronic obliterative disease. In one study fresh occlusions were found in 50 per cent of a group of legs amputated for atherosclerotic gangrene.[2] These thrombi were frequently several centimeters in length and often multiple.

The extent of obstructive atherosclerosis in gangrenous legs as revealed by injection and dissection technics[2] is significantly greater than that found in infarcted hearts examined by similar methods.[5, 6] Comparable studies of the arterial circulation of the kidneys,[7] brain[8] and bowel[8] have indicated that atherosclerosis does not produce in these arterial circuits the extensive obliterative disease found in the leg. These observations suggest that the lower extremity may prove to be the most fertile clinical area in which to study the problem of atherosclerosis.

Interarterial Anastomosis

Despite the clinical importance and the intense interest in arterial disease of the lower extremities, knowledge of the anastomotic circulation in the normal person and in various pathologic states remains incomplete. Although the existence of anastomoses is recognized, their extent, their size, their normal functional significance and the derangements that may occur in disease have only recently been studied in detail. Even though an atheroma or an embolus can produce ischemia by occluding an artery, extensive obliterative disease is usually present before gangrene develops. This discrepancy may be accounted for in part by the fact that the leg arteries, unlike the coronary vessels,[9] have a preformed collateral interarterial network that can immediately compensate for arterial obstruction.[2, 10-12] The main initial impetus to the opening of these collaterals is the augmented differential pressure above and below the sites of occlusion.[11] In addition, arterial narrowing and occlusion lead to an increase in the number and size of these anastomoses.[2, 10, 12, 13] In a series of 56 amputated legs in which 438 distinct occlusions were found, interarterial anastomoses by-passing all but 2 of these obstructions were clearly demonstrated. In almost every such limb one or more anastomoses greater than 0.2 mm. in internal diameter could be visualized.[2] The commonest site for large, grossly visible communications is in the region of the ankle joint. Since most of the occlusive disease is limited to the major vessels between the knee and the ankle, the ankle area is precisely the zone where anastomotic vessels would be most effective. Both experimental and clinical observations have indicated that one of the greatest stimuli to the opening and further enlargement of these anastomotic pathways is the presence of ischemia.[12] Therefore, the answer to why the extremity can tolerate such extensive atherosclerosis without gangrene is that it is capable of developing — at least up to a point — an extremely rich compensatory circulation, which may effectively by-pass a large number of narrowed and occluded arterial segments. Occasionally, the internal diameters of these anastomotic leg vessels approach those of the original major arteries they connect.[2]

The function of any collateral circulation, of course, is to facilitate a flow of blood through the capillaries of the threatened part sufficient not only for nutrition at rest but also for an increased flow when the part is physiologically active. The collateral vessels, however, are rarely if ever as effective as the original system in delivering blood to the periphery. The significance of this may best be understood by reference to two physical laws pertaining to the flow of liquids through rigid tubes of small caliber. The first of these states that resistance to flow varies directly with the frictional surface, or that the effective head of pressure is inversely proportional to the length of the tube. The second, known as Poiseuille's law, states that the volume flow or quantity of fluid passing through a tube per unit time is proportional to the fourth power of the diameter of the tube. If the diameter of an artery is halved, the flow through that vessel is reduced sixteenfold. Thus, if long, narrow collateral vessels are substituted for short, wide arterial pathways, effective pressure and volume flow are diminished. The fact that several collaterals may bridge the gap does not adequately offset these disadvantages because the total cross-sectional area is not sufficiently increased.[14]

The effectiveness of the normally present collateral circulation is enhanced by the fact that the atherosclerotic process involves primarily the main tibial arteries and leaves the branch vessels relatively unscathed. This selective specificity of the disease is most fortunate since it permits the branch arteries to function as anastomotic by-passes when the main stems become obstructed. Thus, if the occlusions in the large arteries are few and small the collateral flow need travel only short distances before returning to the main channel. There is little loss of volume flow and little loss of pressure in overcoming internal resistance, and in time the diameter of such unobstructed collateral vessels may increase and so augment the volume flow. The blood will therefore reach the arterioles in quantity and at high pressure. In this situation pulsatile flow will be restored and prognosis for viability of the limb is good. If arterial blood cannot return to the main arteries because they are blocked by extensive atherosclerosis and thrombosis, the limb will depend for its nutrition and ultimate survival on the lateral and terminal branch-

es. These, because of their small caliber and tremendous length, will only permit blood to reach the arterioles at a low pressure and in reduced quantity: the degree of ischemia will be more severe and the prognosis for survival of the limb much poorer than when the obstruction in the main arteries is less extensive.

The pathologic substrate of occlusion and anastomosis that determines the fate of a limb should not, however, be thought of as a constant and invariable picture. It is a shifting background in which changes frequently occur quite rapidly. Although there is a parallel increase in narrowing and occlusion, narrowing does not necessarily or commonly go on progressively and gradually to occlusion. Instead, the process is periodically accelerated by the sudden development of complete, fresh thrombotic occlusions. Although most of these are distal to sites of old occlusion they play an important role in diminishing the blood supply to the foot. They often plug arterial segments that previously functioned as conduits whereby blood passed from one collateral vessel to another.

Vascular Tone

In the previous discussion reference was made only to the anastomotic interarterial circulation above the level of the arteriole. It is the adequacy of this prearteriolar collateral bed that largely determines the quantity of blood delivered to the arterioles per unit time and therefore the effective blood flow to ischemic tissue. Chambers and Zweifach[15] have redefined the nature of the postarteriolar bed as visualized in the omentum of the dog and the mesoappendix of the rat. They found that smooth-muscle fibers extended beyond the terminal arteriole onto a vessel, the metarteriole, that formed a bridge between arteriole and venule. Capillary loops given off at the proximal end of the metarteriole rejoined the vessel as it approached the venule. A muscular precapillary sphincter was found to be strategically located at the site of origin of the capillary from the metarteriole so that it could regulate capillary inflow.

The metarteriolar wall and the precapillary sphincter are highly sensitive to local changes. Drugs such as epinephrine and histamine may, in appropriate doses, constrict or dilate the metarteriolar wall and precapillary sphincter without affecting the caliber of the arteriolar lumen. In other dosage ranges the precapillary sphincter may be constricted, and the metarteriole lumen unaffected.[15]

In addition to this system, there are direct communications between arterioles and venules, arteriovenous shunts,[16] through which channels the flow of blood may by-pass the capillaries. In man such pathways connecting arterioles and veins of the terminal phalanges have been demonstrated.[17]

Clinically, much importance has been attached to this postarteriolar bed. Although there is little evidence that the arteriolar vessels are in "spasm" in organic arterial insufficiency,[18] it has been assumed that dilatation of this portion of the circulation will improve the nutrition of ischemic tissue. Unfortunately, methods such as measurement of skin-temperature and limb-volume changes do not record effective blood flow but rather increments in the total amount of blood or the rate at which blood passes through a portion of the extremity.[19] There is evidence that sympathetic denervation produces a relaxation of the arteriovenous vasculature as well as of the arteriole-metarteriole-capillary network.[20] Whether it is possible, therefore, to improve effective capillary blood flow by removing normal tone is not at all clear. The hazards of producing generalized vasodilatation when only localized dilatation is desired have been emphasized.[21] The observation that interruption of sympathetic activity may increase skin temperatures does not necessarily imply a similar vasodilatation in deep structures.[22, 23] The reverse has, in fact, been claimed.[24] Some observers[25-27] believe that interruption of normal sympathetic tone (even without producing systemic hypotension) may occasionally aggravate ischemia. Although secondary arterial[28] and venous[29] thrombosis has been implicated, the mechanism whereby such a catastrophe could occur might be from extensive diversion of blood from ischemic tissue through dilated arteriovenous sluices.[20]

Summary

From these observations it is apparent that obstruction of the major peripheral arteries is primarily responsible for the development of ischemia in the leg and that a rich interarterial collateral circulation — in part preformed, in part produced by the ischemia — compensates for this obstruction to arterial flow. It is also evident that the more proximal, the more extensive and the more rapid the obliteration of the major arteries, the more embarrassed the collateral circulation and the more severe the ischemia. Finally, it has been indicated that release of normal tone in the arteriolar and postarteriolar circulation may not necessarily improve effective blood flow to ischemic tissue.

Clinical Aspects of Arterial Insufficiency

Intermittent Claudication

Mechanism. Atherosclerosis, with its predilection for the major arteries of the lower leg, is the commonest cause of intermittent claudication. It is not surprising, therefore, that in the vast majority of patients with this syndrome the pedal pulses should be absent. So constant is this finding that one should be extremely hesitant, in the absence of anemia,[30] to entertain a diagnosis of claudication if both the dorsalis-pedis and posterior-tibial pulses

are full and bounding. Intermittent claudication has probably escaped recognition in severe anemia because it is usually a minor complaint and one that is likely to be grouped among the paresthesias commonly found in anemic patients.[30] Claudication in patients with normal or only partially impaired peripheral arterial pulsations has been attributed to occlusions of the branch arteries supplying important muscle groups[31, 32] and to arteriolar obstruction.[33] Patients, in whom pedal pulses were present, have been observed with claudication secondary to occlusion of an iliac artery[34] or to coarctation of the aorta.[35] In coarctation the velocity of blood flow in the large arteries of the leg is reduced, and the arterial-arteriolar difference in blood pressure greatly diminished.[36] This small arterial-arteriolar difference represents sufficient encroachment on the local circulatory reserve to produce ischemic pain without obliterating the pulse. Boyd and Jepson[34] suggest that in the occasional patient with claudication and palpable pedal pulsations, the occlusion will be found proximal to the femoral artery. In view of the demonstrated occurrence in peripheral atherosclerosis of obstruction of the large arteries and the development of a rich collateral circulation, which could occasionally permit pulsatile flow distal to the occluded area, this explanation[34] appears more reasonable than one that postulates small-vessel obstruction as the sole mechanism.

Some investigators have maintained that spasm alone can produce intermittent claudication. Support for this point of view has centered around the observation that there is often a diminution in the peripheral pulses after exercise in patients with intermittent claudication in whom pedal pulses were palpable at rest.[37-39] Other investigators[40-44] have not found the evidence for spasm at all convincing. Pickering[18] has shown how closely clinical organic vascular narrowing and occlusion may mimic vascular spasm. The two known stimuli producing spasm are trauma and cold. Any artery adequately stimulated mechanically will probably go into spasm. In certain cases of Raynaud's phenomenon an intrinsic inherited peculiarity endows the digital arteries with unduly intense constriction to cold.[18] Horton[35] has emphasized the fact that intermittent claudication is not seen in Raynaud's disease or vasomotor vasoconstriction. Finally, there are no documented cases of intermittent claudication occurring from spasm alone. Lindqvist[45, 46] reported a case with good pedal pulses and claudication that he originally attributed to spasm. Subsequently, he found the etiologic mechanism in this patient to be coarctation of the aorta.[35]

It is now generally accepted that intermittent claudication results from muscular ischemia secondary to arterial occlusive disease in which blood supply is adequate for resting muscle but inadequate when muscle is actively contracting. The oxygen requirement of contracting muscle may increase thirty times above the resting level. This vastly increased requirement is met in part by extraction of more oxygen from each unit of blood passing through the capillaries and in part by an increase in arterial and capillary blood flow. It is the inability of obstructed arteries to deliver this additional blood that produces intermittent claudication.

The precise mechanism whereby the pain of intermittent claudication arises has never been fully elucidated. Kissin[47] has claimed that generalized anoxemia without ischemia can induce pain in an exercising skeletal muscle. Lewis[40] believed that the stimulus to pain arose from intracellular metabolic changes, acted outside the muscle fibers in the tissue spaces and was not the direct result of anoxemia. Katz, Lindner and Landt[48] suggested that the pain-producing substance was a product of metabolic muscular activity, diffused in and out of the blood stream and was nonvolatile and acid. Harpuder and Stein,[49-51] on the basis of experimental and clinical observations, believed that potassium was liberated from the cells and that in ischemia introduced a physical factor that led to the rapid accumulation of potassium ions, thereby providing the necessary stimulus to the pain end organs in muscle.

The paresthesias and sensory and motor changes developing during a period of circulatory arrest to a limb have been described.[52, 53] Marked sensory impairment was always noted long before any perceptible deterioration in motor power. In a recent study of the effect of peripheral ischemia on nerve conduction, it was shown that, among afferent fibers, the more rapid the conduction velocity of the fiber the greater the depressant effect of ischemia. Motor fibers, however, were more resistant to ischemia than certain afferent fibers of slower conduction rate.[54] The different thresholds of various sensory fibers to ischemia may explain why under some circumstances intermittent claudication may be experienced as a pain and at other times as a paresthesia.

Diagnosis. A diagnosis of intermittent claudication may be accepted when physical exertion produces in the foot, calf or thigh pain or cramps promptly relieved by the cessation of the activity:

> Intermittent claudication probably is the most specific symptom in all the list of human ailments. It never occurs in the legs as a result of standing, reclining or sitting, and it has no relationship to muscle cramps which patients have in bed. It is brought on only by continuous exercise and is relieved promptly by discontinuance of exercise without change of position of the affected part.[55]

The clinical picture is frequently complicated by the coexistence of other pathologic conditions, such as neuritis, arthritis, phlebitis, defects in body mechanics and local inflammatory processes, that may cause pain in an extremity. Duryee[56] has discussed this problem in differential diagnosis.

It is important routinely to consider the existence of these other lesions since the symptoms they produce may be more disabling than the claudication itself. To assist further in analysis of the complaint of leg pain several tests have been devised to facilitate the diagnosis of claudication as well as to gauge the severity of the disability and the response to therapy.[57-63] In most cases, however, a carefully taken history and physical examination will clarify the problem.

Pulses. Impairment of the arterial pulsation as noted by simple palpation is the most important and consistent physical finding of occlusive arterial disease. Occasionally, normal peripheral arterial pulsations may not be palpable because the vessels pursue anomalous pathways.[64-66] It is clear, however, that a considerable degree of narrowing and even occlusion can be present in the large arteries without producing detectable reduction in arterial pulsation. The brief course and large diameter of some collateral branches that by-pass short occlusions can easily explain the frequent clinical finding of the return of pulsatile flow distal to a complete occlusion. In such cases one does not expect, and one does not usually find, evidence of ischemia. If a patient complains of pain in the leg and the arterial pulsations are full and bounding, the symptom almost certainly is not due to arterial insufficiency.

Oscillometry. The oscillometer is used clinically as an aid in determining the volume of the pulsation in an extremity. Oscillometry has its main value in confirming the absence of palpable pulses, in demonstrating a difference in pulsatile flow in the two extremities when peripheral pulses cannot be discerned, and in following the progress of the balance between occlusion and anastomotic flow. It is also useful, as an adjunct to the palpation of pulses, in determining the level at which an arterial block has occurred.[67] It is essential to remember that palpation of pulses and oscillometric readings are crude guides to arterial insufficiency and do not accurately reflect the effectiveness of the collateral blood supply.

Arterial calcification. In the past, undue emphasis has been placed on the presence of calcification in the walls of atherosclerotic vessels. The clinical effects of atherosclerosis are not dependent so much on hardening of the vessel as on narrowing or obliteration of the lumen. Calcification is not only inconstant but also, is itself, a relatively benign process causing little if any interference with the flow of blood. Arterial calcification in the lower extremity has been noted frequently in young men free of any symptoms or signs of arterial insufficiency.[68, 69] It is found more often in the male than in the female,[70] and is common in diabetic persons.[71] Arterial calcification is said to be of some diagnostic value in distinguishing between atherosclerosis and thromboangiitis obliterans, in which it is absent or minimal.[70, 72] Possibly, it is only an indication of very early arteriosclerosis. Intimal and medial calcification can perhaps be distinguished on the roentgenogram.[1, 70, 73, 74] When both intimal and medial calcification are present in the same zone, however, even microscopical study cannot always distinguish between them.

It has been claimed[59] that calcified vessels when associated with hypertension show little tendency to thrombosis. Of particular interest are several reports of the lack of correlation between arterial calcification and occlusion[70, 72] and even of an inverse relation between the two.[1] A recent study has clearly demonstrated the absence of any correlation between calcification and occlusion in patients in whom the clinical picture of atherosclerosis and gangrene was sufficiently severe to necessitate amputation.[2] These observations indicate that the taking of a roentgenogram merely to determine whether or not arterial calcification is present does not contribute materially to the diagnosis of intermittent claudication.

Arteriography. It is easy to demonstrate collateral vessels by the injection of radiopaque mediums during life.[13] Since it has not been possible to translate these objective anatomic evidences of collateral flow into functional terms, arteriography cannot be used as a prognostic guide to therapy or as an indication of the paucity, richness or effectiveness of these auxiliary vessels. One does not need an arteriogram to appreciate that collateral circulation must be extensive if major arterial pulsations in the limb are absent and the tissues of the toes are viable. Boyd[59] has indicated that, in his experience, arteriography has never revealed main-vessel block that was not suggested by oscillometry.

It should be recalled that, although occlusions are not rare in the femoral and iliac arteries,[75] the major site of obstruction in atherosclerosis is between the knee and the ankle. It is precisely this bottleneck area that is most difficult to visualize completely even with a good contrast medium. It is much easier both during life and at autopsy to demonstrate the femoral artery, the popliteal artery or the terminations of the anterior and posterior tibial arteries in the foot than to visualize the tibial arteries in the lower leg. The intra-arterial injection of radiopaque mediums, moreover, is not performed without discomfort or risk.[76] Arteriography is a valuable diagnostic aid in operative procedures on obstructed arteries.[77] Knowledge of the localization of the occlusive process and the limits of arteriography should, however, temper any surgical plan to relieve intermittent claudication or other symptoms of ischemia in the atherosclerotic limb by restoring the integrity of the arterial lumen in the thigh.[77-80]

Treatment. If any therapeutic regimen is applied to a group of patients in whom claudication is of

less than one month's duration, one may anticipate better results than if a comparable group is utilized in whom the disability has been present for more than three years. Intermittent claudication has a tendency to improve spontaneously after its onset. Silbert[81] and others[59, 82, 83] have emphasized the fact that significant variations in exercise tolerance occur naturally in the course of the disease. After occlusion of a major artery in an extremity, one may expect an increase in collateral circulation during the first year; this increase may continue for two or three years, independent of therapy.[81] In addition to spontaneous improvement, claudication can occasionally be dramatically relieved by postural changes that throw less strain on affected muscles.[82] Almost invariably, uncomplicated intermittent claudication can be relieved by a reduction in the rate at which the patient walks.[82, 84, 85]

The initial distress of the patient with intermittent claudication is often out of all proportion to the actual disability. This discrepancy is due, in some cases, to the fact that the syndrome represents the first serious physical impairment encountered in a vigorous, active life and one that is envisaged as becoming inexorably more confining as time passes. Others interpret "hardening" of the leg arteries to mean the inevitable spread of vascular disease to other vital organs. Finally, there are those who equate intermittent claudication with gangrene and amputation. The physician who fully appreciates such fears is in an excellent position to help these patients.

In practice, the disability in most patients with intermittent claudication is not profound; only a small percentage have to change their employment because of a limited exercise tolerance. Furthermore, intermittent claudication does not have the same prognostic relation to gangrene and amputation[86] that angina pectoris has to death from myocardial infarction, cardiac arrhythmia or congestive heart failure.[87]

There is today no single effective measure for the treatment of intermittent claudication that has gained wide acceptance. This is not for any lack of ingenuity on the part of workers in the field. Within the last half-century many diverse therapies have been suggested. Drugs investigated have included calcium,[88] vitamin E,[89] theobromine,[90] methyl testosterone,[91] depropanex,[92-94] cytochrome C,[95, 96] intravenous hypertonic saline solution,[97, 98] thiouracil,[59] histamine[99-101] and various sympatholytic agents.[102-108]

Mechanical aids, some of them based on demonstrably favorable physiologic alterations in peripheral blood flow,[109, 110] have included intermittent venous occlusion,[111-113] pavaex[114, 115] and Buerger's exercises.[116, 117]

Surgical procedures have also covered a wide spectrum. It has been recommended that the femoral vein be ligated,[118] that the femoral artery be ligated[119] and that the femoral artery be anastomosed to the femoral vein.[120] More recently, accessible occluded femoral and popliteal segments have been resected and replaced by grafts.[77-79] In addition to this direct attack on the blood vessels themselves, the sympathetic innervation of the lower extremity has been interrupted by periarterial stripping,[121] paravertebral blockade with procaine,[122] alcohol[123] and phenol[59] and extirpation of the lumbar ganglions.[124-129] Finally, division of the external popliteal and posterior tibial nerves and tenotomy of the Achilles tendon have been attempted.[59]

Tobacco. The continued use of tobacco by patients with intermittent claudication is still strongly interdicted.[130, 131] In an excellent monograph, Roth[132] has reviewed her own and other studies on the effects of tobacco on the heart and peripheral circulation. She[133] has presented evidence that peripheral blood vessels in normal human subjects become constricted during smoking. She has also shown that these vascular effects are caused by the nicotine rather than by the mechanics of smoking, the combustion of cigarette paper or the inhalation of substances such as carbon monoxide and the pyridine bases. Analogous changes have been produced in the blood vessels of the extremities by smoking and by the intravenous injection of nicotine.

After subjects had smoked standard cigarettes, it was found that whereas the blood pressure, pulse rate and electrocardiogram returned to normal within five to fifteen minutes, peripheral vascular constriction as indicated by decreased skin temperatures of the extremities persisted from half an hour to an hour and in some cases much longer. Why the peripheral effects of nicotine should persist longer than the cardiac effects is not known. One mechanism whereby the drug may induce this prolonged vasoconstriction was recently suggested by Burn,[133] who demonstrated that smoking, or the intravenous injection of nicotine, could inhibit, in man, the diuresis caused by drinking of water. This inhibition, he believes, is due to release of antidiuretic hormone, which can be found in the urine after smoking.

The fact that tobacco smoking can increase the tone of peripheral vessels is adequate justification for urging all patients with acute arterial insufficiency to stop smoking at least until the imbalance between obstruction and collateral flow has been improved. It is equally justifiable on the basis of a considerable body of clinical data[132, 134] to urge all patients with thromboangiitis obliterans to abstain from tobacco. However, for the large group of ambulatory patients with intermittent claudication from atherosclerosis the need for such a restriction is not so clear.

Experiments designed to produce atherosclerotic changes in the heart and aorta by causing animals to inhale tobacco smoke for long periods or by subcutaneous or intravenous injections of solutions of tobacco for a considerable time have not proved successful.[135] There is no evidence that tobacco, any more than mildly cold weather, adversely affects the course of the disease. Some investigators[83] have been unable to demonstrate any deleterious effects of tobacco on intermittent claudication due to atherosclerosis. Others[136] have permitted patients to smoke a few cigarettes daily without apparent harm. Tobacco smoking in many of these patients is a well entrenched habit. For them abstinence may be neither necessary from the organic point of view nor desirable for emotional reasons. Finally, since the vascular effects of smoking are directly related to the nicotine content[132] it is possible that some of the newer cigarettes said to be low in nicotine content[137] will have such minimal effects on the peripheral circulation that for all practical purposes their influence may be ignored. Further studies in this direction will be most useful.

Summary. To help the patient with intermittent claudication it is necessary to realize that one is measuring a subjective phenomenon, that complicating disease processes may coexist, that the natural history of the syndrome is variable and finally that the significance of the limitation to the individual patient represents an important aspect of the disability.

In summarizing the problem of therapy Kekwick[82] stated: "There can be little doubt that whatever the methods of treatment employed the more encouragement these patients have, the better they do. In the present stage of knowledge, the means used to achieve results should merely satisfy the condition that they will do no harm." Ischemia itself is an effective vasodilator[12] and can cause collateral channels to enlarge.[2] Walking to the limit of pain tolerance — that is, to ischemia — appears to be as safe and effective as any measure yet devised to stimulate the development of collateral vessels. Correction of pathologic states like anemia and congestive heart failure, which increase the disparity between blood supply and demand, and the recognition and treatment of other symptomatic conditions, such as concomitant venous and postural defects, will also alleviate the disability from intermittent claudication.

Prophylaxis and Management of Gangrene

Current conservative management has been largely responsible for the marked decrease in amputations, the successful use of more limited operative procedures[138, 139] and the relatively advanced age at which major amputations are now necessary among patients with occlusive arterial disease. All therapeutic measures aimed at averting or limiting gangrene have as their goal a decrease in the disparity between the supply and demand for blood by ischemic tissue. Any therapeutic procedure diverging from this aim may precipitate necrosis. Gangrene rarely appears *de novo* even in the limb with extensive old arterial obstruction. It usually develops because of the additional burden produced by mechanical, chemical and thermal trauma, infection, congestive heart failure, anemia and fresh arterial occlusion.

Diabetes. The prominence of diabetes among patients with peripheral arteriosclerosis and gangrene is striking.[140 - 143] If glucose tolerance curves are obtained on all patients with arterial occlusive disease and gangrene the incidence of diabetes will be even greater.[144] Since the severity of the diabetic state is not related to the development of gangrene and since in many patients the metabolic defect can be recognized only after examination of the blood sugar, diabetes should be suspected in every patient with peripheral atherosclerosis.[144] It is only in this way that any possible benefits from good management can be realized.[145]

Diabetes may contribute in several ways to peripheral arterial insufficiency. The metabolic disorder is probably associated with an acceleration of the atherosclerotic process itself[146]; it is thus associated with cerebral atherosclerosis and attendant mental changes and with coronary atherosclerosis with resultant congestive heart failure. It is also associated with retinal and peripheral neuropathy,[147] which alters the patient's awareness of local trauma. Finally, resistance to infection may be impaired in diabetic patients.[148]

Foot care and infection. In about half the patients ulceration and gangrene develop as the result of avoidable trauma, unnecessary minor surgery of the toes or the injudicious use of local applications.[144, 149] Detailed instructions for the proper care of the feet have been published.[150] Unnecessary exposure to trauma can be avoided by careful instruction of patients and their families in the minutiae of foot and toenail hygiene, in the importance of properly fitting shoes, in the proper care of calluses and in the avoidance of excessive heat or cold to the extremities. Minor injuries should be reported promptly to the physician, and self-treatment should be discouraged. In the presence of ulceration and gangrene the advantages of bed rest, protective cradles, infrequent dressings[151] and elevation of the head of the bed are clear. Careful and judicious débridement may aid materially in the healing of localized purulent foci. Proteolytic enzymes have recently been recommended as an adjunct in the treatment of necrotic lesions.[152] The true value of these agents, however, remains to be defined.

The appropriate use of a variety of antibiotics in large doses systemically and in appropriate men-

struums locally has perhaps been more responsible than any other single factor for the sharp decline in amputations during recent years. Sensitization to antimicrobial drugs and the dangers of chemically irritating substances used in the treatment of fungous infections must, however, be fully appreciated.

Patients with advanced occlusive disease will usually submit to any number of medical and surgical procedures designed to prevent or treat an ulcerated or gangrenous lesion. The success of any such therapy, however, will vary directly with the willingness and ability of the patient or his family to accept the responsibility for the proper care of his feet.

Congestive heart failure and anemia. The role of congestive heart failure and anemia in aggravating arterial insufficiency perhaps deserves special emphasis. Marked reduction in peripheral blood flow and vasoconstriction occur in advanced congestive heart failure.[153] Reversal of these altered hemodynamics by successful treatment of the congestive heart failure is frequently accompanied by a decrease in the ischemia and an accelerated healing of ulcerated lesions. In anemia the tissues are supplied with oxygen adequate for basal requirements, but the low tissue oxygen tensions result in a diminution of the margin of safety.[154] Thus, in the presence of advanced occlusive disease, even a mild anemia in these elderly patients may decrease this margin of safety sufficiently to tip unfavorably the delicate balance between viability and necrosis. Although it has been demonstrated that anemia may stimulate interarterial anastomoses,[155] it has also been suggested that anemia may predispose to thromboembolism.[156] Once clinical manifestations of ischemia have developed in an extremity, viability will be enhanced by correction rather than maintenance of the anemia. In these elderly patients this can be achieved by multiple small transfusions. It is important, in this regard, to realize that the formed elements of the peripheral blood and bone marrow do not change strikingly as people grow older[157] and that a mild anemia in elderly patients is not a "normal" finding.

Fresh occlusion. From the standpoint of tissue viability it is immaterial whether fresh occlusions are embolic from the heart or represent local thromboses of arterial segments in the leg. The important factors are the location and the length of the occlusion and its potential for propagation. Stasis produced by old occlusions, congestive heart failure or hypotension favors the growth of these thrombi. Usually a small fresh occlusion can be tolerated by the normal or atherosclerotic limb because of a previously formed and rich collateral circulation. An extensive occlusion, however, is dangerous because it blocks the large arteries that are acting as communications between many sets of collateral vessels. Sudden spread of gangrene can occasionally be correlated with the deposition of extensive fresh thrombi.[2] If such catastrophes can be prevented in these patients it is conceivable that their extremities might be salvaged. A major therapeutic attempt should thus be made, in patients with incipient or limited gangrene, to prevent the deposition or extension of fresh occlusions in the main arterial channels. There are a number of experimental studies[158-161] indicating that the development and growth of thrombi may be aborted by anticoagulant therapy. Such therapy, although not without dangers,[162] may be effective in diminishing the necessity for major amputation.

Surgical removal of a recent embolus to prevent gangrene or avert subsequent arterial insufficiency is still recommended,[3, 163, 164] if the patient is seen within a few hours of the occurrence of the embolism. It is, however, frequently difficult to determine clinically whether one is dealing with an embolus or a thrombus, and emboli are not infrequently multiple.[4, 165] Emboli in the popliteal artery and below are not easily accessible, and surgical intervention in the popliteal fossa or above may sever crucial collateral arterial channels. In addition, operative incision of atherosclerotic vessels carries some risk of subsequent thrombosis. Hemorrhage into the arterial wall has been described.[166-168] When an embolus produces ischemia, hemorrhage into a distal atheromatous plaque[169] or thrombosis superimposed on a distal, previously narrowed or occluded segment may further augment the initial arterial insufficiency. Such dynamic changes will not be corrected by embolectomy.

In every patient with arterial embolization leading to gangrene and requiring major amputation at the Beth Israel Hospital during the past five years, extensive propagation of a clot from the embolus was found.[169] Since one cannot predict in which patients extension of a fresh occlusion will occur, the management of choice in most patients with fresh peripheral arterial embolism appears to be adequate anticoagulant therapy.[170] There is some question whether or not aortic embolism is treated more effectively by surgery than by anticoagulants.[171 - 175] However, no controlled study of the two therapies in this condition has yet been reported.

The occurrence of an acute arterial occlusion constitutes a medical emergency. Although anticoagulants are indicated, an ideal drug is not yet available. Dicumarol unquestionably exerts a retarding influence on blood coagulation in vitro [176-178] and on the development of experimental intravascular thrombosis in animals.[159-161, 179-184] In addition, statistical studies in man indicate that it produces a significant reduction in thromboembolism.[185 - 187] It has been reported that a prothrombin concentration of between 5 and 10 per cent, determined by the method of Rosenfield and Tuft,[188] can usually be regarded as safe[189] and that at this level coagulation is retarded.[190] It is not known how effective such levels are against

thrombotic disorders. The delayed action of the drug, the difficulties in controlling the prothrombin concentration and the risk of hemorrhage are well known and have led to the use of newer, similarly acting compounds.[191-195] That thrombosis may occasionally "break through" apparently adequate Dicumarol therapy has been reported.[196] Heparin, with its prompt anticoagulant effect, which can be relatively easily controlled, has been effectively employed for many years.[197] Its use is still limited by the need for parenteral administration. Although various methods of administration have been tried,[198-202] intermittent intravenous injection appears to be the most satisfactory despite wide swings in the clotting time.

There is some experimental evidence that substances such as Dicumarol that depress prothrombin conversion may not provide as optimal an anticoagulant effect as heparin,[161, 203] which blocks fibrin deposition through other mechanisms.[204 - 207] At present heparin in considered the drug of choice in the short-term treatment of acute arterial occlusion. Recently, the use of indwelling catheters and needles has been recommended in the administration of intermittent injection of heparin at frequent intervals over two-week periods.[208] If such technics prove feasible in clinical practice, they will facilitate the use of heparin in the treatment of sudden arterial embolism and thrombosis.

Alteration of vascular tone. Much interest exists clinically in the potential value of interrupting sympathetic tone either medically or surgically in the prophylaxis and treatment of gangrene. Systemically administered vasodilators may cause vasodilatation throughout the body, thereby defeating their purpose.[21] It is clear that there is a relatively greater "resistance" to interruption of sympathetic tone in the lower as compared to the upper extremity. This resistance may require the use of relatively large dosages of sympatholytic agents, with resulting hypotension and tachycardia. In patients with coronary-artery disease such disturbances in hemodynamics may precipitate myocardial ischemia and even necrosis.[209, 210] It is essential to recall the high incidence of coronary-artery disease among elderly diabetic persons[211] as well as the fact that many patients may have coronary-artery obstruction without clinical manifestations.[212] In the great majority of patients with impending or actual gangrene, therefore, the systemic use of vasodilator drugs is probably contraindicated.

There have been several reports of the value of intra-arterial vasodilators in the management of advanced peripheral arteriosclerosis.[100, 101, 108] This route of administration, it has been claimed, will minimize the systemic effects of the drugs. Recently, however, intra-arterial injection of Priscoline has also been found to cause myocardial infarction.[213] Intra-arterial therapy, requiring as it does, repeated arterial puncture, invites, of course, the risk of thrombosis in sclerotic arteries.[213] The value of such therapy in patients with advanced obliterative disease remains to be established.

Surgical denervation of the sympathetic system has been claimed to produce a local vasodilatation and a healing of ulcerated lesions.[128, 129, 214] Yet lumbar sympathectomy also causes a response in the entire extremity. As mentioned above, there is inadequate evidence that effective nutritional blood flow is increased by this procedure. Finally, experimental and clinical data are accumulating that in a large majority of patients, return of sympathetic tone occurs within months of the operative procedure,[215-220] even though the foot may remain warm.[217] These observations tend to invalidate the claim that sympathectomy has any "prophylactic" value in the prevention of gangrene.[221]

Summary. In a recent study gangrene was found to develop most commonly in the elderly, mentally disturbed patient with mild diabetes, peripheral neuropathy and absent pulsations distal to the femoral arteries.[144] Almost invariably two or more conditions such as extensive fresh peripheral occlusions, congestive heart failure, anemia, shock, local injury and infection aggravated the circulatory imbalance.[144] Although providing a useful frame of reference, these criteria may be of little prognostic help in individual cases because of inability to assess quantitatively the extent of the occlusive disease and of the local injury. Patients who appear inevitably headed for a major amputation occasionally escape such an outcome with prolonged and diligent conservative management. Conversely, even in the presence of proved minimal occlusive disease a severe, neglected insult to the leg may result in extensive gangrene and amputation even in the presence of pedal pulsations.[144]

It is a curious fact that in the heart, where occlusions are small, comparatively few in number and preformed anastomoses rare, current therapeutic trends have emphasized the value of anticoagulants rather than measures designed to stimulate the collateral circulation. In the leg, on the other hand, where occlusions are extensive and a relatively adequate anastomotic circulation is already present, most of the effort has been designed to stimulate collateral circulation, and little to prevent the main channels from becoming more extensively occluded.

The major threats to viability of the ischemic limb come from the sudden extension of fresh occlusion and the imposing of excessive demands upon a compromised circulation. At present the former may be treated by anti-coagulant therapy and the latter by prophylaxis and vigorous treatment of infection, anemia and other factors that increase local metabolic demands. Today, short of a cure of atherosclerosis, prophylaxis remains the real

key to therapy. By ensuring proper care of his feet, the patient and his physician, rather than the extent of the occlusive disease per se, will largely determine the incidence of gangrene and amputation.

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MEDICAL INTELLIGENCE

DOCTORS AFIELD

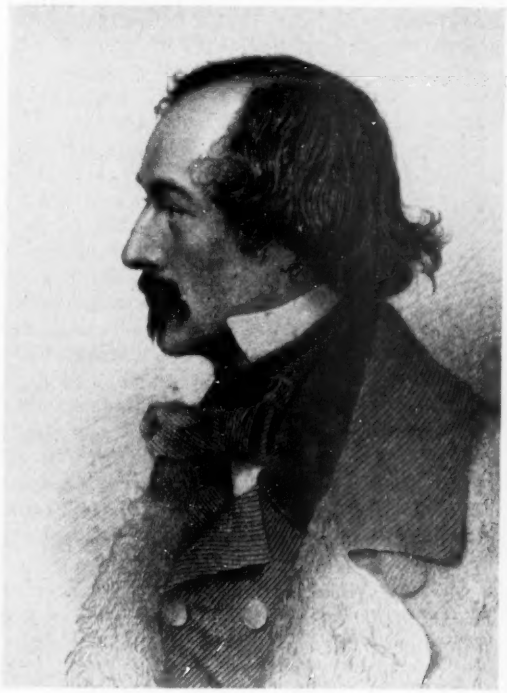
Elisha Kent Kane, Physician and Explorer

HENRY H. FERTIG, M.D.*

CLEVELAND, OHIO

THE name of Elisha Kent Kane is one of which all Americans can be proud, and from his life physicians in particular can gain lasting inspiration. His great-grandmother received training as a surgeon in London in 1749 and, after coming to the colonies, did much to alleviate the suffering of the American prisoners in the Philadelphia prison during the British occupation. Kane was born in Philadelphia on February 3, 1820. As a youth, "he manifested no extraordinary love of learning," and rebelled against the systematic method of study in the schools. At the age of sixteen, when he was attempting to enter Yale, he was found to have rheumatic heart disease, an illness that, with the acute exacerbations of rheumatic fever, was frequently to plague him for the rest of his life. His college studies at the University of Virginia were permanently interrupted at the age of eighteen by an acute attack of rheumatic fever and rheumatic endocarditis. He was brought back home and, wrapped in blankets, remained critically ill for a long while. It was at this time that his father uttered the words that seemed to be his guiding light and a source of strength throughout the adventure-filled years ahead: "Elisha, if you must die, die in the harness."

Going on the assumption that he would be happier if he understood and could treat himself, he turned to the study of medicine rather than continue his training for an engineering career. After a two-year preceptorship, he became a resident physician at Blockley in Philadelphia at the age of twenty-one. His senior there, Dr. McPheeters, stated that at the time, "he was laboring under a serious organic affection of the heart — dilatation with valvular disease, which gave rise to a very loud bruit de soufflet (bellows sound), accompanied by the most tumultuous action of the heart from any violent exertion." Six months later, in 1841, he became a senior resident physician and in March, 1842, he received his diploma from the University of Pennsylvania. After his graduation his father secretly



arranged for him to take the examination for the post of surgeon in the Navy. Although he was not enthusiastic about the idea, he passed his examination and was accepted despite his heart disease. There was no vacancy, however, for an assistant surgeon at that time.

Arrangements were then made with the Secretary of the Navy for him to be appointed physician to the American Embassy in China without endangering his rank in the Navy. He set sail in May, 1843. His adventurous spirit soon led him to resign his

*Curator, Howard Dittrick Museum of Historical Medicine, Cleveland Medical Library.

post and to begin the private practice of medicine in Whampoa, outside Canton. After about six months, however, in 1844, he was stricken with "rice-fever" and became very seriously ill. He then decided to return home and see the world on the way. His deeds and adventures remind one of the late Richard Halliburton, though his motives were sounder.

He remained home for one winter (1845–46), during which Congress declared war with Mexico. Three weeks previously he had been commissioned by the Navy and ordered to Africa. In a comparatively short time he contracted "coast-fever" and had to be sent home. By November 6, 1847, he was on his way to Mexico with a secret message to the American general who had recently captured Mexico City. There were further exciting adventures and a hard struggle with tetanus, which he fortunately won after the administration of 22 grains of opium and the loss of 40 ounces of blood.

For several years, the world was wondering about the fate of the Arctic explorer, Sir John Franklin, and his crew, who had last been seen by a whaler in Baffin Bay in July, 1845. Two vessels offered by Mr. Grinnell, of New York, were attached to and outfitted by the Navy to aid in the search for the English explorer. Dr. Kane was assigned to the brig *Advance* as the senior medical officer, and Dr. Vreeland to the brig *Rescue*. The ships left New York on May 22, 1850. The commander of this expedition feared for Kane's health and offered to send him back to the United States on an English transport, but Kane would have none of it. He subsequently distinguished himself as one of the most efficient and hardest-working men on the voyage. They returned on September 30, 1851. His personal narrative of the journey as told in *The United States Grinnell Expedition in Search of Sir John Franklin* became the official history of the search.

Believing that Franklin and his crew could still be alive, he was no sooner home than he began preparations for his second Arctic expedition, this time under his own command. In the promotion of his plans for this adventure, he spent over a year and a half in hard and at times discouraging labor, interrupted by several attacks of inflammatory rheumatism. He donated his own full pay, amounting to approximately $3,000, and the proceeds of his lecture tours during the winters of 1852 and 1853.

He sailed again on May 30, 1853, to continue the search of two years before. In a letter to his father written on July 23, 1853, he says: "I am not entirely well, but as well as I would be at home, and so trusting in the Great Disposer of good and ill that I am willing to meet like a man the worst that can happen to one secure of right and approving, heart and soul, of that in which he is engaged." Dr. Hayes, surgeon of the expedition, was frequently called to see Kane during the winter of 1853–54 for attacks of severe paroxysmal nocturnal dyspnea. Scurvy repeatedly plagued all the men, and several members of the crew died as a result of disease and exposure. When they failed to return home by the time a second winter had set in, it was feared they too might be lost. In the spring of 1855, the Navy dispatched two vessels to look for them. Kane's brother, Dr. John K. Kane, was one of the volunteers. After untold hardships, which included a 1300-mile trip in an open boat, the survivors of the crew were found by the search party. They landed safely in New York on October 11, 1855. Kane published an account of this expedition in *Arctic Explorations: The second Grinnell expedition in search of Sir John Franklin, 1853, '54, '55*. These volumes are illustrated with 300 engravings from his own sketches made on the spot. Most of the ice studies were in pen-and-ink outlines, with a wash of the same material for a background. Of the hundreds of such sketches, "many were made in the open air, under a killing temperature, by a sick man, with the broad shoulders" of his companions for an easel and with lead pencils for implements. Despite these conditions, all the sketches were notable because of the faithfulness with which he portrayed the scenes before him.

A sick man, he characteristically rose above his physical ailments and sailed for England on October 10, 1856. Here he was honored for his exploits, and while in London he visited Lady Franklin. Unable to stand the heavy London fogs, he found his condition rapidly deteriorating. He was at this time a semi-invalid and decided to seek a warmer climate on the advice of Dr. Watson and Sir Henry Holland. Cuba was the place determined upon, and he left England in November. On his way to St. Thomas he suffered from acute polyarthritis, with fever and night sweats. After a temporary improvement he sailed for Havana and while at sea on December 21, suffered what was probably a cerebral embolism, with aphasia and right hemiplegia. He landed in Havana on Christmas, and by the end of the month had improved considerably. In the midst of preparations to return home, he was suddenly seized with another cerebral attack on February 10 and died quietly six days later, at the early age of thirty-seven. His life echoed his own words: "Call it fatalism, as you ignorantly may, there is that in the story of every eventful life which teaches the inefficiency of human means and the *present* control of a Supreme agency."

Carnegie Medical Building

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39321

PRESENTATION OF CASE

A thirty-three-year-old single woman was admitted to the hospital for arthroplasty of the left hip.

She had had an acute infection in the left hip at the age of nine months, for which two operations had been performed. Postoperatively, she was kept in a cast for several months, and ever since she had had a stiff hip. Because of increasing pain in the left hip, thigh and knee over the past five years she came to the hospital.

There was no history of tuberculosis. Ten years before admission, after a period of recurrent midepigastric pain, a gastrointestinal series was taken and was said to have shown a duodenal ulcer. This apparently responded to medical treatment, and the patient had since been free of symptoms. One year before entry she had a partial hysterectomy, uterine suspension and appendectomy because of dysmenorrhea.

Physical examination showed a slightly overweight woman who appeared in good general health. The left hip was fixed in 60° flexion, 20° adduction and 20° internal rotation. The left leg was 9.5 cm. shorter than the right. There was marked lumbar lordosis. The examination was otherwise negative.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 85 diastolic.

Urinalysis was negative. The blood hemoglobin was 14.4 gm. per 100 cc., and the white-cell count 9300, with a normal differential.

On the seventh hospital day an uneventful cup arthroplasty of the left hip was performed, during which the patient received two transfusions. After operation the temperature curve was irregular, with daily elevations to about 101°F. A blood hemoglobin determination on the fourth postoperative day was 11.0 gm. per 100 cc. On the sixth postoperative day, about an hour and a half after a meal of spaghetti she noted a dull, aching, nonradiating epigastric pain, became nauseated and vomited yellowish material. The pain increased in severity, with radiation in girdle fashion across the abdomen but not through to the back. Later, it was localized to the right upper quadrant. It was not clear whether or not the pain was similar to the one that she had experienced ten years before admission. Pain and vomiting persisted throughout the night and the following morning. Physical examination revealed a soft, nondistended abdomen, with no spasm or rigidity. Tenderness was most severe in the epigastrium but was moderate across the abdomen in girdle distribution just above the umbilicus. Peristalsis was slightly more active than normal but was otherwise unremarkable. The white-cell count was 16,400, the hemoglobin 10 gm. per 100 cc., and the serum amylase 14 units per 100 cc. She improved with sedation, Gelusil and a bland diet, but later in the day physical examination showed the abdomen to be distended and tympanitic. There was slightly increased resistance in the right upper quadrant, with slight tenderness. Peristalsis was diminished, with occasional tinkles, which were rare in the upper quadrants. During the following night she again had minimal epigastric pain but considerable nausea and repeated vomiting of large quantities of fluid,

FIGURE 1. *Roentgenogram of the Abdomen.*
Note the marked gaseous distention of the stomach and proximal portion of the duodenum.

as well as a bloating epigastric discomfort. There was now marked abdominal distention, with tympany in the upper abdomen, especially in the epigastrium and left hypochondrium. There was no tenderness on respiration, and Murphy's sign was not present. No abdominal spasm was noted. High-pitched tinkles were heard on auscultation of the epigastrium and left upper quadrant. Examination of the chest was negative. The white-cell count was now 21,800.

A plain film of the abdomen revealed tremendous dilatation of the stomach (Fig. 1). Superimposed on the antral shadow was a dilated segment of upper small bowel. There was a small amount of gas in the large bowel.

Eight days after the first operation another operation was performed.

Differential Diagnosis

Dr. Leland S. McKittrick*: Before picking a few of the findings, I should like to have the whole picture, which would include the x-ray findings.

Dr. John F. Gibbons: This film of the pelvis taken immediately after admission shows the markedly deformed femur, with no recognizable head and neck remaining and with a dysplastic acetabulum; the upward riding of the femoral shaft; and the deformity of the pelvis, which would explain the fact that the left leg was shorter than the right. In the films taken after the operation, the cup in the newly made acetabulum is demonstrated. The chest film is entirely normal. The film of the abdomen shows a greatly distended stomach (Fig. 1). Through the antral portion of the stomach one can vaguely see a distended loop of small bowel, which is probably the descending limb of the duodenum. There is no gas in the remaining portion of the small bowel, but there is a fair amount of gas in the distal colon and rectum. There are no abnormal soft-tissue masses that I can see.

Dr. McKittrick: My interpretation of this film is that the patient obviously had a dilatation of the stomach and swallowed air. She did not have a complete acute small-bowel obstruction because she had too much gas in the descending colon and rectum. I think that is as far as I can go with this film.

Dr. Gibbons: I should agree with that.

Dr. McKittrick: Just to go back over this briefly and try to pick up a few points: supposedly, for what it may be worth, this woman had a duodenal ulcer. The hemoglobin was normal on admission and was 11 gm. per 100 cc. on the fourth postoperative day although she had two transfusions during operation; I am not sure that that is of any significance. I do not know how much blood a heavy-set person loses during an operation such as this, but I should think the lowered hemoglobin was a perfectly legitimate situation. She ran a temperature of 101°F. during the early postoperative period. I should suppose that anybody who ran such a temperature after operation had something the matter. I am not sure that I can connect that with what followed, but I cannot overlook it.

On the sixth postoperative day she had some spaghetti and after that she had dull nonradiating epigastric pain, which became worse, and she vomited yellowish material. This pain was steady and increased in severity, with a sort of girdle radiation, but did not go straight through into the back. Later on there was more pain on the right side. I think I can assume that something new had come into the picture at that time. My first reaction is to attempt to correlate that something new with the slight fever or the operation; I must confess I find it very difficult to associate the two. For the moment, therefore, I am going to assume that the something new was not a direct complication of the operation itself or of the condition causing the fever that occurred after the operation.

The next question is, What does that attack of pain suggest? It in no way suggests a small-bowel obstruction to me because the onset of pain was not sudden and the pain was not colicky. It had no relation to the duodenal ulcer because there was not a penetration or perforation of that ulcer. This woman had not had any recent symptoms from the ulcer. I am content, since the character of the pain was not sudden, severe and sharp, and the physical examination was negative, to overlook the fact that she had the duodenal ulcer.

The pain suggests more strongly than anything else pain referable to the biliary tree, and the symptoms were perfectly consistent with biliary-tract disease. The pain was dull at first, and grew worse and worse; the patient became nauseated, and vomited larger amounts of material than one would have expected her to vomit. The negative physical examination is entirely in keeping with an attack of gallstone colic. She was seen early in the attack; she was a heavy-set woman whose gall bladder was probably high; therefore, I would not be surprised at an entirely negative physical examination early in the attack. But the pain persisted; that makes me throw out a simple so-called gallstone attack. Pain with gallstones may become so severe that the patient is given morphine after which the pain disappears spontaneously. The fact that this patient's pain persisted means that it cannot be explained on the basis of an uncomplicated attack of gallstones.

There is not as much information in the protocol as I should like, but probably there is all that would be helpful. The patient continued to have not severe pain but a certain amount of distress, and she vomited quite a lot. The record does not say how much, or what the character of the vomitus was. I think it is significant that the symptoms persisted, and it may be significant that she became

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more distended, that the white-cell count rose to 16,000 and that she had tenderness across the abdomen. Midepigastric tenderness was mentioned. I do not know how anybody else interprets midabdominal tenderness, but I do not even palpate in the midabdomen for tenderness because I do not think anyone can interpret tenderness felt over the great vessels. To me midepigastric tenderness alone means nothing whatsoever. Tenderness to mean anything to me must be on either one side or the other of the midline so I shall disregard that midepigastric tenderness. I shall not disregard the statement that she had some tenderness running across the abdomen. That tenderness was present on the left just as well as it was on the right. If true this is really significant.

How am I going to add all these symptoms up? The pain, I gather, was quite severe to begin with. Its severity lessened, but some discomfort persisted. The patient vomited a good deal. She never had any real abdominal spasm, but she had tenderness in the epigastrium, which I shall overlook, and in the left hypochondrium, which I shall not overlook. She had one attack that started as a gallstone attack would but did not let up as a simple gallstone attack should have done. The symptoms persisted. She had no localizing signs, and she had distention with at first tenderness across the stomach and then definite tenderness in the left hypochondrium. The white-cell count rose to 21,000, and the serum amylase was 14 units. I find it very difficult, with those symptoms, to make an intelligent differential diagnosis because I do not know what to include. The only diagnosis that I can make, which I am sure is the wrong one, is acute pancreatitis. I am excluding acute cholecystitis because to make such a diagnosis reasonable tenderness localized in the right upper quadrant and probably muscle spasm or a mass should have been present.

Why do I say acute pancreatitis? The attack of pain suggesting gallstones, the persistence of pain and the absence of localizing signs in the right upper quadrant, but with tenderness in the left hypogastrium, are in keeping with pancreatitis. The serum amylase is not, but I do not think this alone negates the diagnosis. I have to make a diagnosis, and I feel compelled to come up with that. I am sure everyone is aware of a situation that is disturbing many of us — that is, the association of acute pancreatitis with operations. We see it more frequently with operations on the stomach, particularly resections, and sometimes with operations on the biliary tree; in a few cases pancreatitis has been a postoperative complication of or at least associated with surgery other than abdominal surgery. Dunphy, Brooks and Achroyd* recently reviewed the records of a group of patients with postoperative pancreatitis at the Peter Bent Brigham Hospital; I believe it occurred in 1 or 2 cases after thyroidectomy, although most of them followed abdominal operations. The mechanism is not understood.

At least there is a background for pancreatitis although that diagnosis probably is not justified on the evidence that I have before me. Having been thinking rather simply in a straight line in this case, and having no other acceptable diagnosis, I am compelled to end up by saying the only diagnosis I can make is acute pancreatitis.

DR. CHESTER M. JONES: Dr. McKittrick, would you be willing to say that although it is impossible to make an absolute diagnosis here, it is more important to make a decision to do something?

DR. MCKITTRICK: That is true. Every once in a while one is forced to make the decision for or against operation, sometimes without a diagnosis; perhaps that was the situation here. If, on seeing this patient, I had made the diagnosis of acute pancreatitis, I should not have operated on her.

DR. TALMAGE W. NIELSEN: Is that large amount of vomiting consistent with a diagnosis of pancreatitis?

DR. MCKITTRICK: No; it bothers me.

DR. NIELSEN: I think the patient vomited about 2000 cc. in the basin at one sitting.

DR. MCKITTRICK: I did not know that. It is not characteristic of pancreatitis. Patients with pancreatitis characteristically are nauseated, feel they cannot eat and may vomit a little at a time but characteristically do not vomit as much as this patient did. That makes me wonder whether she had an acute dilatation of the stomach, with the point of atony probably extending to the superior mesenteric vessels, but there is nothing in the record to indicate the type or total amount of vomitus; therefore, I cannot end up with that diagnosis.

DR. NIELSEN: Is this much vomiting consistent with an acute cholecystitis?

DR. MCKITTRICK: No. There is nothing about this case, if the findings were accurately elicited and recorded, that warrants a diagnosis of acute cholecystitis.

DR. MELVIN J. GLIMCHER: Three points were not brought out or made clear. The first is that this patient was on streptomycin and penicillin therapy for the entire postoperative period because of the cup arthroplasty. This was a critical point, which helped shape the service diagnosis. The second is that the distention developed in the morning after the second episode of pain during the night. The first episode of pain occurred in the evening. In the morning she was put on an ulcer regimen, and the pain completely cleared up and she was free of symptoms and did not vomit. During the following night pain and nausea and some vomiting recurred, and the next morning she began to vomit

*Dunphy, J. E., Brooks, J. R., and Achroyd, F. Acute postoperative pancreatitis. *New Eng. J. Med.* **248**:445-451, 1953.

large amounts of yellowish material; she became very distended and had high-pitched tinkles in the left epigastrium and upper abdomen. The third point is that the left-upper-quadrant tenderness was present only throughout the first night; it did not persist in the left hypochondrium, and was never a prominent feature of the physical examination.

DR. MCKITTRICK: These good friends are trying to talk me into making the correct diagnosis, but they are not making any headway, because I still do not know.

CLINICAL DIAGNOSIS

?Small-bowel obstruction.

Acute cholecystitis with impaction of gall-bladder ampulla in foramen of Winslow (after preoperative medication).

DR. LELAND S. MCKITTRICK'S DIAGNOSIS

?Acute pancreatitis.

ANATOMICAL DIAGNOSIS

Acute cholecystitis with impaction of gall-bladder ampulla in foramen of Winslow.

PATHOLOGICAL DISCUSSION

DR. WILLIAM P. J. PEETE: At the time the patient went down to the operating room it was thought that she had an acute small-bowel obstruction. When she received medication, of course, we examined her again, and I thought I could make out a small mass in the right upper quadrant. In addition we knew that she had received penicillin and streptomycin so we reasoned preoperatively that she had acute cholecystitis with an impaction of the ampulla of the gall bladder into the foramen of Winslow. I have seen other gall bladders with a flabby ampulla; this was distended and accounted for obstruction of the duodenum here. That is what she did have at operation.

DR. MCKITTRICK: That was perfectly all right. I cannot consistently make a diagnosis of acute cholecystitis with diffuse upper abdominal symptoms. The symptoms must localize in the right upper quadrant. Otherwise, there must be some other explanation. The explanation for this patient's symptoms must have been a complication. Since the symptoms did not localize, I chose the next commonest diagnosis, pancreatitis, with which the symptoms are more diffuse. The vomiting was wrong for both of them.

DR. PEETE: That is why we postulated an obstruction in addition to the acute cholecystitis. I think if you had seen the patient you would have agreed.

DR. WINFIELD S. MORGAN: The gall bladder was removed; it measured about 8 cm. long and 8 cm. in circumference, was dark greenish purple and contained stones. Microscopically, it showed an acute inflammation, with gangrene.

DR. MCKITTRICK: Was the gall bladder high in position?

DR. PEETE: No; it was bound down very tightly by the peritoneum overlying it.

DR. MCKITTRICK: Was it below the costal margin?

DR. PEETE: No; it was at the costal margin.

CASE 39322

PRESENTATION OF CASE

A sixty-one-year-old woman was admitted to the hospital because of progressive weakness, edema and shortness of breath for three weeks.

The patient was in good health until seventeen years before entry, when a severe left-sided pneumonia complicated by three days of anuria or oliguria and followed by ankle edema developed. One year later she was again admitted to the hospital because of another episode of pneumonia of the left lower lobe (Type 7 pneumococcus), with auricular fibrillation at a rate of 160, requiring digitalization. Later in the illness an aortic systolic murmur was heard. The blood pressure was 130 systolic, 70 diastolic. There was albuminuria during the febrile period, but this later cleared. Argyria was noted. The cardiac rhythm reverted to normal after recovery from pneumonia. Since this episode of pneumonia she had noted a heart murmur, which she could hear and feel. Nine years before admission while she was under anesthesia for a pelvic repair, the blood pressure suddenly dropped, and the operation had to be discontinued. She did well until twenty-one months before admission, when she first noted exertional dyspnea. Shortly afterward, while climbing stairs, she fainted for the first time, and she again fainted ten days later while climbing stairs. She had since been maintained on digitoxin and had improved with bed rest and digitalization. Three months before admission she noted a pressure sensation in the sternum and epigastrium associated with a cold. She also had ankle edema. Her physician found the liver to be enlarged. She improved after ten days of bed rest but had led a bed-to-chair existence ever since. For the past month she had had increasing weakness, dyspnea, anorexia, ankle edema and weight loss. Along with digitoxin and a low-sodium diet she received Mercuhydrin injections, with only slight increase in urinary output. She stated that she was no longer able to hear or feel the heart murmur.

She had a history of using argyrol nose drops for upper respiratory infections for over nine years and had had argyria for many years.

On physical examination the patient had moderate dyspnea and orthopnea. The skin was a bluish-gray color consistent with argyria. The neck veins were distended. The lung bases were dull, with scattered, fine rales. The heart was enlarged,

the border extending 12 cm. to the left of the midsternal line. The cardiac rhythm was regular, with occasional runs of rapid, regular beats. There was a Grade 4 aortic systolic murmur, with a Grade 4 thrill transmitted to the neck vessels, and a Grade 3 aortic diastolic murmur transmitted downward and backward. The aortic second sound was absent. Heart sounds at the apex were of poor quality. The liver edge was not felt although the liver was ballotted 3 fingerbreadths below the costal margin. There was +++ ankle edema and ++ sacral edema.

The temperature was 97.8°F., the pulse 80, and the respirations 18. The blood pressure was 110 systolic, 95 diastolic.

A urine specimen had a specific gravity of 1.018 and gave a ++ test for albumin; the sediment contained 250 white cells per high-power field. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 cc. and a white-cell count of 14,800, with 86 per cent neutrophils. The serum nonprotein nitrogen was 70 mg., the total protein 5.5 gm., the albumin 2.9 gm., and the globulin 2.6 gm. per 100 cc. The sodium was 139 milliequiv., the chloride 101 milliequiv., the carbon dioxide 34 milliequiv., and the potassium 5.8 milliequiv. per liter. A roentgenogram of the chest revealed great enlargement of the heart shadow, which almost reached to the left chest wall (Fig. 1). It was believed that the left ventricle and possibly the right ventricle were enlarged. The aorta was moderately tortuous, and the hilar and pulmonary vascular shadows were engorged. There was a considerable amount of fluid in the left pleural space. An electrocardiogram showed a bizarre record in which there was a dissociation of the auricular and ventricular rhythms, both regular, and a shifting intraventricular conduction.

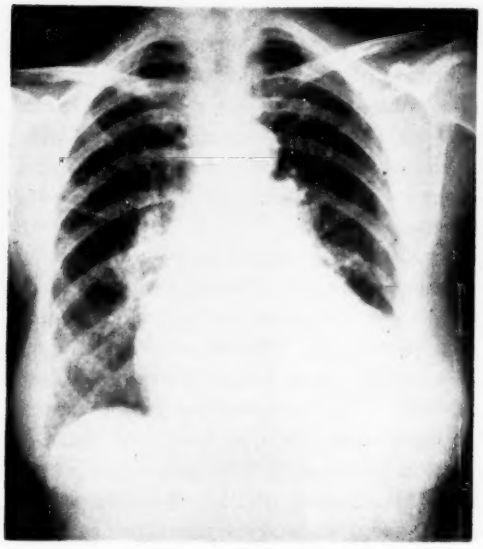

FIGURE 1. *Roentgenogram of the Chest.*
Note the cardiac enlargement, chiefly of the left ventricle, small pleural effusion, left base, and moderate engorgement of the pulmonary vessels.

In the hospital, the patient initially responded to diuretics with loss of weight but after about two weeks again began to retain fluid. A second electrocardiogram on the tenth hospital day revealed auricular fibrillation. The temperature, pulse and respiration during this period, however, were normal. On the seventeenth hospital day she complained of considerable dyspnea. She denied chest pain. On physical examination there was auricular fibrillation at a rate of 130. The neck veins were distended, there were signs of a small left pleural effusion, and there were rales at the right base. The blood pressure was 110 systolic, 95 diastolic. The temperature was 99°F., and the pulse 120. She was given an extra dose of digitalis, but on the next day she was more dyspneic; there were moist rales over both bases extending up to the angles of the scapulas. She was coughing up small amounts of frothy material. During the next week her condition was about the same, with little change in the lung findings. The temperature was irregular, the highest elevation being 100°F.; the pulse varied from 70 to 140. On the twenty-fifth hospital day the aortic diastolic murmur was louder than the aortic systolic whereas previously the reverse had been true. The patient became lethargic and oliguric, and terminally she was comatose and had irregular respirations. On the thirtieth hospital day while being turned in bed she suddenly died.

Differential Diagnosis

DR. ALLAN L. FRIEDLICH*: I should like to resolve this patient's problems into three parts; the first problem seems to be concerned with the two episodes of pneumonia seventeen and sixteen years before admission. If she had been a child, I might consider the fact that repeated respiratory infections and pneumonia are quite common in persons with large left to right shunts, such as one sees in defect of the atrial septum or patent ductus arteriosus. Were those episodes of pneumonia related in any way to subsequent events? We have become skeptical about the diagnosis of pneumonia for two reasons. At times pulmonary edema may be confused with a virus pneumonia; and we have become much more sensitive to the possibility of pulmonary infarcts, which may simulate the clinical picture of pneumonococcus pneumonia. Two findings tend to point in the direction of pulmonary infarction as the cause of the second episode of pneumonia; one is the onset of auricular fibrillation, and the other the fact that edema of the ankles followed that

*Assistant in medicine, Massachusetts General Hospital.

episode. But in this case a pathogenic pneumococcus was isolated, and in the absence of any further information I have to assume that she had pneumococcal pneumonia. The transient albuminuria and oliguria are probably consistent with the febrile reaction, although acute glomerulonephritis may occur after pneumococcal infection. The urinary findings do not substantiate that. An interesting point is the apparent temporal relation between the second bout of pneumonia and the onset of the loud systolic murmur, which the patient was able to feel and to hear. If such an episode had occurred in recent years, I should consider the possibility that she had contracted a pneumococcal endocarditis, which was then cured and left a scarred aortic valve. Because this episode occurred at least sixteen years ago, before penicillin was available, the statistical likelihood of her being able to survive a bout of acute bacterial endocarditis is almost nil. In conclusion I should think in all probability that the two episodes of pneumonia bore no relation to subsequent events.

The second problem is to determine the nature of the structural abnormality in the heart causing the aortic murmur. The description is certainly that of aortic stenosis and regurgitation. Occasionally, other conditions are confused with this one. In coarctation of the aorta a diastolic element to the murmur may be present, but if the blood pressure was measured in the right arm rather than the left, I can assume by the absence of hypertension that a coarctation was not present. The murmur of patent ductus arteriosus may also be confused with that of aortic stenosis and regurgitation, but here again the narrow pulse pressure virtually rules that out. There are a few rare possibilities that we might consider such as a dissection of the aorta with a double-barreled aorta. There was no history of pain, and a story of sixteen years' duration is long for dissection of the aorta, as well as for a ball-valve thrombus in the left ventricle resulting from an old myocardial infarct and obstructing the aortic valve. I think we can eliminate both possibilities.

There was no history to suggest a congenital aortic stenosis. She may have had a congenital bicuspid aortic valve, which is not an uncommon condition and which may be associated with premature deposition of calcium and the development of aortic stenosis. Another remote possibility is syphilitic aortic aneurysm that produced the systolic murmur, the diastolic murmur being due to the aortic regurgitation on the same basis. It would be unusual for the systolic murmur to be of this intensity with an aortic aneurysm. Is there any report about the serology?

Dr. Winfield S. Morgan: I can find no note in the record of a serology report.

Dr. Friedlich: I believe that the most likely explanation is that this patient had rheumatic heart disease with aortic stenosis and regurgitation, probably with a high degree of stenosis and a slighter degree of regurgitation as judged by the fact that the diastolic pressure was well maintained. This would explain a number of the features of her disease. In the first place she had a number of fainting episodes, which are common in severe aortic stenosis but are also common in pulmonary embolism. She had progressive symptoms and signs of failure first of the left and then of the right ventricle. She had an extraordinarily narrow pulse pressure of only 15 mm. of mercury, which is suggestive of severe aortic stenosis. The loud murmur and thrill with transmission up the neck veins, the absent aortic second sound and the aortic diastolic murmur are all characteristic.

May I look at the x-ray films of the chest?

Dr. John F. Gibbons: The heart is enlarged; apparently the left ventricle is the most enlarged of the chambers (Fig. 1). The fluoroscopist thought the right ventricle was also probably enlarged. There is a suggestion of a double shadow in the anteroposterior view, which would make it seem that the left atrium is also slightly enlarged. The aorta is tortuous in its ascending portion. The knob is apparently of normal size and contains some calcium. The descending aorta as seen here is wide, and there is a small bulge of the arch as it starts downward. There is fluid in the posterior part of the left lung base. The protocol stated that the amount was considerable; I do not think there was very much fluid. The pulmonary vessels are moderately engorged.

Dr. Friedlich: Did the fluoroscopist see any calcification in the aortic valves?

Dr. Gibbons: No; he did not mention any, and I do not see any on the films. There is a small scar in the upper lobe that may have been due to the old pneumonia.

Dr. Friedlich: Do you think there was sufficient dilatation of the aorta really to constitute a proper aneurysm? It is more in line with senile ectasia.

DR. GIBBONS: I think it is not unusual to have a bulge like this in an aorta that is quite wide and tortuous.

DR. FRIEDLICH: The third problem, which is the hardest of all, is whether the course of the terminal illness can be explained solely on the basis of the pre-existing mechanical cardiac difficulty. The patient had a severe degree of aortic disease — I am postulating the onset of failure almost two years before entry with temporary improvement on digitalis. She then had an inexorably downhill course, with progression of congestive heart failure for three months before death. This is consistent with the presence of severe aortic disease. In patients with rheumatic valve disease who die in congestive heart failure even at this late age, Gross* pointed out some years ago, that Aschoff bodies, if carefully searched for, may be found in quite a high proportion of cases — at least in those in which there is not another cause for congestive heart failure. It is conceivable that the combination of the valvular defect and active rheumatic fever even at this age would be possible. The electrocardiogram in this case is not much help to me. I assume that the dissociation between the atria and ventricles was not of the complete atrioventricular variety because the pulse rate was not slow enough for that. Therefore I suspect that the patient had a variety of nodal rhythm in which the rate of the atrioventricular node was a little faster than that of the atrium and that the phenomenon known as interference and dissociation was present. This is seen under a variety of circumstances, most frequently with vagal stimulation or with excess digitalis.

Several features of the course, however, make me suspect that something else was going on. An isolated pleural effusion on the left is uncommon in congestive heart failure, and this makes one suspect pulmonary embolism. Additional suggestive evidence of pulmonary emboli are the elevated white-cell count, the occurrence of fainting episodes and the occurrence of rapid auricular fibrillation. However, we have no positive evidence of pulmonary infarction.

The patient certainly had some renal disease. There were white cells in the urine, albuminuria, a high nonprotein nitrogen, a high potassium level and oliguria. The sodium level was normal so that I cannot ascribe these findings to the so-called low-sodium syndrome. I am concerned, in addition to the underlying cardiac disease, about the possibility of subacute bacterial endocarditis. I should like to consider that because it is an especially insidious disease in elderly patients; it is easily overlooked, and it can explain several things. In the first place the rapid downhill course followed a respiratory infection, and a history of preceding respiratory infections is even more common in subacute bacterial endocarditis than a history of tooth extraction. She had weight loss that must have been considerable because she lost weight while she was putting on edema; that would fit with bacterial endocarditis or equally well with an extensive hidden neoplasm, for which again there was no evidence. There is a suggestion in the record that one of two things may have happened: either the aortic systolic murmur became less, which is not uncommon as failure progresses, or the murmur of aortic regurgitation became more prominent; but I think it is a minor point. A more important point is that she had evidence of renal insufficiency, which could be explained by a focal embolic glomerulonephritis or a diffuse glomerulonephritis, both of which may also accompany subacute bacterial endocarditis. There are many points against subacute bacterial endocarditis. She had almost no fever, no splinter hemorrhages under the fingernails, no clubbing and no splenomegaly; nevertheless, I favor this possibility. I think it should be considered strongly, particularly because it is a potentially remediable disease. I am left with the impression that the patient had argyria, rheumatic heart disease, with aortic stenosis of a severe degree and slight aortic regurgitation, severe congestive heart failure and subacute bacterial endocarditis, with renal impairment on that basis.

A PHYSICIAN: Do you think there is a relation between argyria and the cardiac status?

DR. FRIEDLICH: No; only when it is misinterpreted as congenital heart disease.

DR. LELAND S. MCKITTRICK: Why did she die suddenly?

DR. FRIEDLICH: Patients with aortic stenosis do die suddenly. From the description of the terminal illness her death did not seem to be very sudden; she seemed to have been quite sick for a long time.

DR. CHESTER M. JONES: Is it not unusual to have a subacute bacterial endocarditis with this

*Gross, L., and Ehrlich, J. C. Studies on myocardial Aschoff body. II. Life cycle, sites of predilection and relation to clinical course of rheumatic fever. *Am. J. Path.* **10**:489-504, 1934.

degree of renal involvement and to have no red cells in the urine? I think that casts reasonable doubt on the diagnosis. Could a mural thrombus have been the cause of sudden death? She apparently died suddenly as she was being turned in bed.

DR. FRIEDLICH: That was one of the things that I considered. The other thing that may have played a role is invasion of the ventricular septum by calcific deposits extending from the calcified aortic valve. This can produce Stokes–Adams attacks.

CLINICAL DIAGNOSIS

Rheumatic heart disease, with aortic stenosis and insufficiency.
?Bacterial endocarditis.

DR. ALLAN F. FRIEDLICH'S DIAGNOSES

Rheumatic heart disease, with severe aortic stenosis and slight aortic regurgitation.
Subacute bacterial endocarditis, with renal failure.
Congestive heart failure.
Argyria.

ANATOMICAL DIAGNOSES

Calcific aortic stenosis.
Pulmonary embolism and infarction.
Mural thrombi, both atria.
Nephrosclerosis.

PATHOLOGICAL DISCUSSION

DR. MORGAN: At autopsy the lungs were surprisingly clear of congestion or edema and weighed about 700 gm. The branch of the pulmonary artery supplying the left lower lobe was partially occluded by adherent mottled red and gray emboli, and there were two infarcts in the left lower lobe, the largest of which measured 3 cm. in greatest dimension. These were brownish and microscopically showed advanced stages of organization, which would be consistent with the acute episode of dyspnea that occurred about thirteen days before death. The pericardial sac contained about 100 cc. of clear, serous fluid but was otherwise not remarkable. The heart was much enlarged and dilated, weighing 510 gm. There was a severe calcific aortic stenosis, the aortic lumen being fixed and measuring about 1 cm. long and 0.3 cm. across. There was no bacterial endocarditis, and all three of the aortic cusps were identified. Aside from moderate calcification of the annulus the mitral valve was completely normal. There were mural thrombi in both atria, those in the right undoubtedly having given rise to the pulmonary emboli. The kidneys did not appear as severely affected as we might have expected from the clinical story; there was moderately severe nephrosclerosis and some evidence of old pyelonephritis but nothing acute. Two incidental findings were several small ulcers in the transverse colon, six or more, and an area of fat necrosis in the pancreas. The etiology of these we cannot definitely explain, but it may have been on the basis of small emboli. There were no embolic changes in the kidneys.

DR. FRIEDLICH: What was the nature of the pleural fluid? Could we have established the diagnosis if it had been withdrawn before death?

DR. MORGAN: This was a small loculated collection of clear, serous fluid.

DR. FRIEDLICH: That does not help.

A PHYSICIAN: Were there Aschoff bodies?

DR. MORGAN: There were focal areas of fibrosis in the myocardium that we usually consider to be on the basis of ischemia, but we found no evidence of changes that we might attribute to old rheumatic disease and there were no Aschoff bodies.

The question of the etiology of calcific aortic stenosis is, of course, one that has been argued for many years, one school believing that the changes in the aortic valve were due to arteriosclerosis, and the other that they indicated previous rheumatic endocarditis or some bacterial infection. Most recent authors have concluded that the disease was rheumatic in origin. In the case under discussion, we believed that the severity of the pneumonia sixteen years before admission and the time relation of development of cardiac findings strongly suggested that the patient had a pneumococcal endocarditis of the aortic valve coincident with her bout of pneumonia, from which she recovered but from which the calcific aortic stenosis developed.

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HEALTH PROGRAM FOR FEDERAL EMPLOYEES

A HEALTH program for federal employees was established by action of the Seventy-Ninth Congress in 1946 (Public Law 658). The program got under way in 1948 and has recently been transferred to the Department of Health, Education and Welfare under the direction of Dr. Joseph Weisskopf.

Approximately 50,000 persons are covered by this program and its degree of utilization is high, 40,000 persons (not necessarily representing the original 50,000 covered, since the personnel is to some extent transient) having participated. The two major objectives of the program are to serve the federal employee by helping him to retain optimal health while on the job, and to serve the employer (the Government, including all taxpayers) by increasing or continuing production through the establishment and maintenance of methods and standards that make it possible for the employee to remain in optimal health in his total work environment.

No attempt is made to give medical care. The system is patterned on that used in private industry. Emergency care is provided for those injured on the job. Employees needing medical or surgical attention are referred to private physicians and dentists.

The various governmental agencies are authorized to establish this program and to allow the sum of $9 per person per year in their budgets to pay for it. When possible, public-health nurses and physicians are utilized. The employee's own physician is given all necessary information. In case of an occupational injury, federal facilities for treatment are available, and full medical care is given.

There has been little or no opposition by the profession to this plan when it has been completely understood. There is no effort to supplement or to interfere with private practice. Indeed, it is said that private practice is increased by the health program. At the present time in the Boston area only the general services such as the housekeeping services at the post office are included.

A copy of the law and a statement of the policy of administration together with certain data concerning experience during the past five years are on file in the office of the Director of Medical Information and Education of the Massachusetts Medical Society, and may be consulted by interested fellows.

AN ANTIVIRAL SUBSTANCE DERIVED FROM A PENICILLIUM

THE term "broad spectrum" has been applied to certain antibiotics because they are active against both gram-positive and gram-negative bacteria and also against rickettsias and some viruses. The implication of the "antiviral activity" of these drugs (as distinct from their antirickettsial action) has often been interpreted literally, particularly by uncritical clinicians, to indicate effectiveness against all viruses when, in fact, their only significant anti-

viral action, both in laboratory animals and in human patients, has been limited to the large viruses of the psittacosis-trachoma-lymphogranuloma venereum group. Recently, Shope* described a substance derived from a culture of *Penicillium funiculosum* that appeared to exert a favorable effect against infections with small viruses.

The cultures of *P. funiculosum* when first isolated proved capable of elaborating a substance that exerted a favorable therapeutic effect against infections with the swine influenza virus in white mice. Those cultures, however, were extremely variable and irregular in their production of the antiviral substance, and during maintenance in the laboratory for several years gradually lost this property. Efforts to restore it were unsuccessful.

Subsequently, it was found that the mold elaborated a substance therapeutically effective against Columbia SK encephalomyelitis virus infection in mice. This new substance appears to differ from the earlier one that was active against the swine influenza virus, but it was found to exert an even greater therapeutic effect against Semliki Forest virus infections of mice than against the Columbia SK virus. The ultimate significance of this discovery is difficult to assess at present, for the studies reported do not go beyond the description of the properties of the agent and its effectiveness in mice against the viruses mentioned. If it does nothing else, however, it should serve to bolster the morale and courage of the many frustrated workers in this field who have thus far been unsuccessful in similar efforts to find active substances against the "true" viruses.

Of some interest is the source of the organism that produces the new antiviral substance and its designation. It is to be recalled that the strain of penicillium that led to the discovery of penicillin was isolated as a contaminant on an agar plate on which a culture of staphylococcus had grown. Fleming's curiosity had been aroused because of the clear zone of lysis of the staphylococcal colonies surrounding the growth of the contaminating mold. Most of the other well known antibiotic agents — including the earlier enzyme that decomposes the capsular polysaccharides of Type 3 pneumococcus, gramicidin, streptomycin, chloramphenicol, aureomycin, terramycin and erythromycin — were products of systematic studies of micro-organisms derived from soil. The soil samples were usually collected from places where the decomposition of organic matter was expected to take place (namely, from heavily manured or mulched fields, from peat bogs or various composts of grains, grasses or leaves). All these were specifically screened with the express purpose of finding antimicrobial substances or the organisms that might produce them. The names of these active agents were usually chosen so as to connote the organisms from which they were derived, their activity, chemical structure, or even the places where they originated, except for bacitracin, which was named after the patient from whom the antibiotic-producing organism was isolated.

The organism that produces the new antiviral substance was isolated by Shope from the isinglass cover of a photograph of his wife Helen, on Guam, near the end of the war in 1945. To designate this substance in terms less cumbersome and more specific than "antiviral substance or material," Shope named it helenine. This name was selected, "partly because it is non-descriptive and non-committal . . . but largely out of recognition of the good taste shown by the mold producing the substance in locating on the picture of my wife, Helen, at the time of its isolation." It is to be hoped that helenine will be the forerunner of other really useful and effective antiviral agents, better than launching any number of ships or burning Ilium's towers, however high.

*Shope, R. E. Antiviral substance from *Penicillium funiculosum*. *J. Exper. Med.* 97:601-650, 1953.

"LOOK MUMMY; NO HANDS"

MAY to October, the Metropolitan Life Insurance Company reports, is that period of the year so felicitous in many ways when two thirds of the country's 600 bicycle fatalities occur. The motor car, of course, is an all-season and all-weather hazard; dry roads and mild weather now bring to the streets and highways the surprising total of 21,000,000 bicyclists — more than double the prewar number of the anachronistic free-wheelers.

Additional data produced by the Metropolitan statisticians indicate that 90 per cent of the deaths are among males and 70 per cent are of boys between the ages of five and nineteen. Eighty per cent of the fatalities are the result of collisions with motor vehicles, the remainder being due to falls, running into fixed objects, collisions with railroad trains and fatalities among pedestrians.

On the whole, the fantastic eccentricities of progression in which cyclists indulge are mainly responsible for the mishaps to which they are susceptible. Cutting in, crossing traffic lanes and carrying extra passengers on a bicycle built for one are contributory causes to these preventable disasters. No statistics are available on the number of nervous breakdowns occasioned among motor-vehicle operators by these butterflies of the open road.

In the course of a recent conversation with a medical gentleman, he expressed a regret that we had not a heavy Journal in New England, in which articles of fifty pages or more in length could have insertion.

Boston M. & S. J., *August 10, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COGSWELL — George P. Cogswell, M.D., of Cambridge, died on July 14. He was in his eighty-seventh year.

Dr. Cogswell received his degree from Harvard Medical School in 1893. He was senior physician at Mount Auburn Hospital for many years. He was a fellow of the American Medical Association.

He is survived by a daughter, a son, eight grandchildren and a great-grandchild.

JOHNSON — Leighton F. Johnson, M.D., of Brookline, died on July 21. He was in his sixty-third year.

Dr. Johnson received his degree from Boston University School of Medicine in 1915. He was chief of the Department of Oto-laryngology, Massachusetts Memorial Hospitals, and professor of otolaryngology, Boston University School of Medicine. He was a former president of the Norfolk District Medical Society, a fellow of the American Medical Association, a fellow of the American Academy of Ophthalmology and Oto-Laryngology and the American College of Surgeons and a member of the American Laryngological Association and the New England Oto-Laryngological Society. He was recently elected president of the American Bronchoscopic Society.

Dr. Johnson is survived by his widow, two sons, two sisters and a brother.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1953

RÉSUMÉ

DISEASE	JUNE 1953	JUNE 1952	SEVEN-YEAR MEDIAN
Chancroid	1	5	4
Chicken pox	1410	1276	1512
Diphtheria	3	0	21
Dog bite	1426	1772	1594
Dysentery, bacillary	14	2	2
Encephalitis, infectious	4	4	4
German measles	821	3031	437
Gonorrhea	177	155	254
Granuloma, inguinale	1	0	0
Hepatitis, infectious	70	13	4†
Lymphogranuloma venereum	1	1	1
Malaria	1	23	8
Measles	351	2963	2963
Meningitis, meningococcal	10	9	4
Meningitis, Pfeiffer bacillus	3	5	5
Meningitis, pneumococcal	1	3	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	2	3
Mumps	1637	573	888
Poliomyelitis	7	4	4
Salmonellosis	7	18	8
Scarlet fever	268*	247	385
Syphilis	154	148	203
Trichinosis	3	2	2
Tuberculosis, pulmonary	179	146	188
Tuberculosis, other forms	9	10	13
Typhoid fever	5	0	2
Undulant fever	4	1	2
Whooping cough	150	98	466

*Includes streptococcal sore throat.

†Four-year median.

COMMENT

Diseases below the seven-year median included chicken pox, diphtheria, measles, scarlet fever and whooping cough.

Three cases of diphtheria were reported in June. This brings the total number of cases for the six months since January 1 to only 15, the lowest figure for the corresponding period in any year in the history of this state.

The 351 cases of measles reported make this the lowest recorded figure, by a considerable margin, for the month of June.

With but one exception (1952) the figure of 268 reported cases of scarlet fever was the lowest for the month of June since 1912.

Diseases above the seven-year median were bacillary dysentery, German measles, infectious hepatitis (four-year median), meningococcal meningitis and mumps.

Because infectious hepatitis has been a reportable disease only since 1949, the increase noted above can be attributed primarily to more complete reporting. As a result, a more accurate estimate of the endemic incidence of the disease can be obtained.

Since mumps is fairly prevalent in the beginning of the poliomyelitis season, cases of mumps meningitis are likely to be mistaken for poliomyelitis. The meningitis can occur even in the absence of swelling of the parotid glands.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Diphtheria: Boston, 2; New Bedford, 1; total, 3.

Dysentery, bacillary: Boston, 4; Brockton, 2; Hingham, 2; Shrewsbury, 1; Woburn, 1; Worcester, 4; total, 14.

Encephalitis, infectious: Fitchburg, 1; Milton, 1; Somerset, 1; Worcester, 1; total, 4.

Hepatitis, infectious: Auburn, 1; Belchertown, 2; Boston, 17; Cambridge, 1; Chicopee, 2; Douglas, 1; Fitchburg, 1; Fort Devens, 1; Lowell, 2; Millbury, 4; Natick, 1; Needham, 1; Newton, 1; North Adams, 1; Somerset, 1; Springfield, 6; Sutton, 1; Warren, 1; Wellesley, 1; Worcester, 22; Wrentham, 2; total, 70.

Lymphocytic choriomeningitis: Medford, 1.

Malaria: Fort Devens, 1.

Meningitis, meningococcal: Arlington, 1; Boston, 1; Carver, 1; Montague, 1; North Brookfield, 1; Springfield, 1; Stoneham, 1; Topsfield, 1; Wilmington, 2; total, 10.

Meningitis, Pfeiffer bacillus: Natick, 1; Stoughton, 1; West Newbury, 1; total, 3.

Meningitis, pneumococcal: Holyoke, 1.
Meningitis, undetermined: Cambridge, 1; Fitchburg, 1; Marblehead, 1; Quincy, 1; total, 4.
Poliomyelitis: Chelsea, 1; East Longmeadow, 2; Haverhill, 2; Oxford, 1; Stoneham, 1; total, 7.
Salmonellosis: Boston, 1; Shrewsbury, 1; Springfield, 1; Waltham, 1; Woburn, 1; Worcester, 2; total, 7.
Tetanus: Boston, 1.
Trichinosis: Boston, 1; Springfield, 1; Weston, 1; total, 3.
Typhoid fever: Boston, 1; Hampden, 1; New Bedford, 1; Shrewsbury, 1; Weymouth, 1; total, 5.
Undulant fever: Easton, 1; Pittsfield, 1; Upton, 2; total, 4.

CORRESPONDENCE

ANAPHYLAXIS TO INTRAMUSCULAR INJECTION OF PENICILLIN IN OIL

To the Editor: On February 25, 1953, a seventy-year-old woman with emphysema and compensated congestive heart failure received an intramuscular injection of 400,000 units of penicillin in oil for a severe respiratory infection. She had had a lobectomy for bronchiectasis four years previously, when she had been given numerous intramuscular injections of penicillin with no untoward result. She had received penicillin since that time by injection and orally two years ago, but none since. She was on a maintenance dose of 0.1 mg. of digitoxin daily and a low-sodium diet.

The patient was acutely ill, with a temperature of 101.4°F. The ears and pharynx were normal. She was edentulous. Medium moist rales were heard in both lung fields. The cardiac border was in the sixth left interspace, about 1 cm. outside the midclavicular line. The apical rate was 100. The rhythm was regular, and there were no thrills. There was a Grade 2 systolic murmur at the apex. The blood pressure was 146/90. No presacral or peripheral edema was observed. The liver was not palpable.

She was given 400,000 units of Wyeth's Lentopen Pectinated, All-Purpose, Procaine Penicillin and Crystalline Penicillin in Oil intramuscularly in a 1-cc. cartridge (this type of injection does not permit aspiration of blood to see if a vein has been entered). Within two minutes she complained of an unpleasant sensation in her tongue and a squeezing pain in her chest radiating to the arms. Urgent dyspnea rapidly developed, followed by vascular collapse and unconsciousness. She was given 0.5 cc. of a 1:1000 solution of epinephrine hydrochloride by vein. Ten minutes later the pulse was improved in quality, and apnea, which had resulted, disappeared and respiration improved. She was given oxygen by face mask. Ten minutes after the first injection of epinephrine, because the pulse was still of poor quality and respirations were still embarrassed, she was given another 0.5 cc. of epinephrine. She rapidly improved and half an hour after the onset the heart rate was 120, regular and of better volume; the blood pressure was 60 systolic, 30 diastolic. The quality of the heart sounds improved. Moist rales persisted over both lung fields. The patient regained consciousness and complained of a squeezing chest pain. She became intensely pink and restless and vomited several times. She was given 0.06 gm. (1 gr.) of sodium phenobarbital intramuscularly and her restlessness and vomiting gradually subsided. About two hours later an electrocardiogram taken at her home gave no evidence of myocardial infarction.

She was removed to the Winthrop Community Hospital by ambulance. On admission she was quite restless, and another 0.06 gm. of sodium phenobarbital ("aqueous") was given intramuscularly. She relaxed and slept quietly. The temperature over the next forty-eight hours rose to 103°F. by mouth. She appeared quite ill. A repeated electrocardiogram gave no evidence of infarction. She was given sulfadiazine 1 gm. every four hours, and the fever gradually subsided, reaching normal three days later. About thirty-six hours after the injection of penicillin a generalized maculopapular rash that was considered allergic developed. The sulfadiazine was stopped. Pyribenzamine, in a dosage of 50 mg. four times a day, was begun; the rash disappeared forty-eight hours later. The patient gradually improved. X-ray films of the chest showed no pneumonia or congestive heart failure, but revealed emphysema and rib defects on the left, where the lobectomy had been performed, and heart enlargement.

On the fifteenth day she was sufficiently recovered to be discharged. The white-cell count on the morning after admission was 12,400, with 79 per cent neutrophils and no increase in eosinophils. On the fourth day the count dropped to 7000, with 70 per cent neutrophils and no eosinophils. Examination of urine was within normal limits.

Several months later a skin test was performed in my office. She was given 250 units of an aqueous suspension of penicillin G intradermally. Within two minutes a huge wheal developed at the site of injection, followed within two minutes more by giant hives over the body and extremities, and at the end of six minutes dyspnea, cough, marked pallor and a rapid thready pulse occurred. She was immediately given 0.8 cc. of a 1:1000 solution of epinephrine intramuscularly. Within fifteen minutes she had markedly improved. The pulse rate was 100, bounding and regular; the blood pressure was 70 systolic, 90 diastolic. Cough and dyspnea had disappeared. This was followed by an injection of 1 cc. of Histadyl, and at the end of forty-five minutes, except for some shakiness, the patient appeared and felt well.

H. B. Greenfield, M.D.

Winthrop, Mass.

Dr. Greenfield's letter was reviewed by Dr. William Elias, technical director, and by Dr. G. E. Farrar, Jr., medical director, Wyeth Antibiotic Laboratories, as follows:

We take issue with Dr. Greenfield's statements that use of Lentopen All-Purpose in Tubex does not permit aspiration of blood to see if a vein has been entered. When Tubex was devised, this feature was tested and aspirated blood was demonstrable. Recently, another test was performed with blood plainly visible after aspiration, as evidenced by the enclosed Tubex. Tests for aspiration utilize blood from the rabbit heart.

The case described by Dr. Greenfield emphasizes the desirability of determining a possibly dangerous degree of sensitivity in a patient with a history of previous multiple injections of penicillin. Fortunately, anaphylaxis to penicillin is rare. However, Feinberg et al., in an article entitled "Penicillin Anaphylaxis, Nonfatal and Fatal Reactions" (*J.A.M.A.* **152**:114-119, 1953), call it to the attention of physicians, and the concern of the Food and Drug Administration is shown by that agency's continued refusal to permit removal of penicillin from prescription requirements and its recent edict requiring all manufacturers to add the following warning to their literature:

> The injection of penicillin in rare cases may cause acute anaphylaxis. The reaction appears to occur more frequently in patients with bronchial asthma or other allergies, or those who have previously demonstrated a sensitivity to penicillin. Care should be taken to avoid accidental intravenous administration, and resuscitative drugs, such as epinephrine, antihistamines and aminophylline, should be readily available for emergency intravenous administration.

To avoid anaphylactic sensitivity, an intradermal test might be made with soluble penicillin with a concentration of 100 units per cubic centimeter. If intradermal testing is not feasible or penicillin administration is considered imperative in the face of possible sensitivity, a test intramuscular dose of soluble penicillin might be given with a tourniquet applied proximal to the site, with epinephrine ready for injection if needed.

Safety precautions take time and are a nuisance to the busy practitioner. However, we believe they are indicated to avoid fatal or near-fatal reactions in sensitized persons.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Familial Nonreagenic Food-Allergy. By Arthur F. Coca, M.D. Third edition. 8°, cloth, 279 pp., with 21 illustrations and 48 tables. Springfield, Illinois: Charles C Thomas, 1953. $10.50.

This new edition of a book first published in 1942 has been revised to include important material, appearing since the issue of the second edition in 1945. References are carried as footnotes on the various pages, and there are indexes of authors and subjects. The book should be in all collections on allergy.

Blood Clotting and Allied Problems: Transactions of the Fifth Conference, January 21 and 22, 1952, New York, New York. Edited by Joseph E. Flynn, M.D., associate professor of pathology, Columbia University College of Physicians and Surgeons. 8°, cloth, 368 pp., with 148 illustrations. New York: Josiah Macy, Jr. Foundation, 1952. $4.95.

Eight papers were read at this important conference on the new anticoagulants, comparative evaluation of Tromexan and Dicumarol, defects in hemostasis, pathogenesis of irradiation hemorrhage, antithromboplastin activity, fibrinolysin and antifibrinolysin, and the synonymy of the nonprothrombin plasma factors.

Prospects in Psychiatric Research: The proceedings of the Oxford Conference of the Mental Health Research Fund, March 1952. Edited by J. M. Tanner. 8°, cloth, 197 pp., with 4 illustrations. Oxford: Blackwell Scientific Publications, 1953. $4.75. (Distributed by Charles C Thomas, Springfield, Illinois.)

This three-day conference was attended by 49 persons. The topics discussed included ignorance in anatomy and physiology, biochemistry, endocrinology and pharmacology, interaction between the individual and culture, and studies of animal behavior. The text concludes with an article entitled "A Survey of Needs and Opportunities." There is a 6-page bibliography and a good index. The monograph should be in collections on psychiatry and psychology.

Textbook of Virology for Students and Practitioners of Medicine. By A. J. Rhodes, M.D., F.R.C.P. (Edin.), research associate, Connaught Medical Research Laboratories, professor of virus infections, School of Hygiene, University of Toronto, and virologist, Hospital for Sick Children, Toronto; and C. E. van Rooyen, M.D., D.Sc. (Edin.), M.R.C.P. (Lond.), research member, Connaught Medical Research Laboratories, and professor of virus infections, School of Hygiene, University of Toronto. Second edition. 8°, cloth, 561 pp., with 74 illustrations. Baltimore: Williams and Wilkins, 1953. $8.00.

The authors have revised this edition of a special book, first printed in 1949, to bring the text up to date. Several chapters have been extensively revised, and much material has been added, especially on the treatment of virus and rickettsial diseases and on laboratory diagnostic procedures. Lists of selected references have been added to the chapters for the first time, and there is a good index. The book should be in all collections on the subject.

Oestrogens and Neoplasia. By Harold Burrows and Eric S. Horning. With contributions by W. C. J. Ross and C. W. Shoppee. 8°, cloth, 189 pp., with 42 tables and 59 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $6.75.

The authors discuss the relation of the estrogens and tumor formation, with emphasis on tumors, including cancer, of the sexual organs in women and men. A bibliography of 15 pages is appended to the text; there is a good index, and the publishing is excellent (the printing was done in Great Britain). The book should be in all collections on tumors.

Hormonal and Neurogenic Cardiovascular Disorders: Endocrine and neuro-endocrine factors in pathogenesis and treatment. By Wilhelm Raab, M.D., professor of experimental medicine, and head, Cardiovascular Research Unit, Bishop DeGoesbriand Hospital, consulting internist, Mary Fletcher Hospital, Burlington, Vermont, and Placid Memorial Hospital, Lake Placid, New York. 8°, cloth, 722 pp., with 86 illustrations and 21 tables. Baltimore: Williams and Wilkins, 1953. $15.00.

Dr. Raab has written this book for the purpose of pointing out the interrelations and the overlapping of endocrinology and cardioangiology. The text is divided into three parts: experimental cardiovascular effects of hormones and neurohormones; cardiovascular features in endocrine and neuroendocrine syndromes; and endocrine and neuroendocrine factors in cardiovascular syndromes. A comprehensive survey has been made of the pertinent literature, and an extensive bibliography of 3726 titles concludes the text. There is a good index, and the book is well published. It should be in all medical libraries and in collections on endocrinology and cardiology.

The Story of the Adaptation Syndrome (Told in the form of informal, illustrated lectures). By Hans Selye, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), professor and director, Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal. 8°, paper, 225 pp., with illustrations. Montreal, Canada: Acta, Incorporated, 1952. $4.50.

Dr. Selye, in a series of seven lectures, presents an informal, simplified explanation of his investigations and theories on stress and disease and the adaptation syndrome.

The Permeability of Natural Membranes. By Hugh Davson, D.Sc. (Lond.), scientific staff, Medical Research Council, London; and J. F. Danielli, D.Sc., Ph.D., A.R.I.C., professor of zoology, King's College, London. With a foreword by E. Newton Harvey, professor of physiology in Princeton University. Second edition. 8°, cloth, 365 pp., with 73 illustrations and 62 tables. Cambridge: University Press, 1952. 30 sh.

This authoritative text was first published in 1943 and went out of print within a year. This second edition is a reprinting with a few minor additions. Lists of references are appended to the text; there is a good index, and the publishing is excellent. This monograph in the field of cell physiology should be in all collections on biology and physiology.

The Basis of Clinical Neurology: The anatomy and physiology of the nervous system in their application to clinical neurology. By Samuel Brock, M.D., professor of neurology, New York University College of Medicine. Third edition. 8°, cloth, 510 pp., with 124 illustrations and 20 tables. Baltimore: Williams and Wilkins, 1953. $7.00.

This book, first published in 1937, has gone through 7 printings and editions and has been translated into Portuguese and Spanish. This new edition has been thoroughly revised and brought up to date since the publication of the second edition in 1945. There is a bibliography of 15 pages and a good index, and the publishing is excellent. The book should be in all collections on neurology.

Neurosurgery in General Practice. By Adrien Ver Brugghen, M.B., Ch.M., M.S., clinical professor of neurologic surgery (Rush), University of Illinois College of Medicine, and neurosurgeon, Presbyterian Hospital of Chicago. 8°, cloth, 665 pp., with 282 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $14.00.

This new book on neurosurgery was written primarily for the general practitioner, who is most likely to be the first to see patients with injuries to the nervous system. The subject is completely covered, including injuries and diseases of the head and brain, spinal cord, nerves and sympathetic nervous system. The text throughout contains case histories illustrating various conditions. Short lists of references are appended to the chapters, and there is a good index. The book should be in all collections on the subject.

Psychiatric Dictionary with Encyclopedic Treatment of Modern Terms. By Leland E. Hinsie, M.D., and Jacob Shatzky, Ph.D., research librarian, New York State Psychiatric Institute and Hospital. Second edition, with supplement. 8°, cloth, 780 pp. New York: Oxford University Press, 1953. $15.00.

This new edition of an important dictionary first published in 1940 has been brought up to date by the authors and 9 collaborators, who have examined all new words and terms coming into the field of psychiatry since the publication of the first edition. The publishing is excellent. The book is recommended for all medical and general libraries and to all persons interested in the subject.

Friend of the People: The life of Dr. Peter Fayssoux of Charleston, South Carolina. By Chalmers G. Davidson. 12°, cloth, 151 pp. Columbia, South Carolina: Medical Association of South Carolina, 1950. $2.75.

Dr. Fayssoux, a Huguenot, was a prominent physician and patriot. He lived in Charleston, South Carolina, was surgeon-general and chief physician of the Southern Hospital during the Revolution, first president of the Medical Association of South Carolina and an antifederalist, the States' righters of their day. This interesting story should be in all collections on biography, medical and general.

Operative Neurosurgery: With emphasis on procedures in trauma. By Elisha S. Gurdjian, M.D., professor of neurosurgery, Wayne University College of Medicine, and chief, University Neurosurgical Service, Grace Hospital, Detroit; and John E. Webster, M.D., assistant professor of surgery, Wayne University College of Medicine, and University Neurosurgical Service, Grace Hospital, Detroit. 4°, cloth, 422 pp., with 129 illustrations. Baltimore: Williams and Wilkins, 1952. $10.00.

This new book is essentially an atlas, with 129 full-page plates and descriptive text. The material is divided into four sections on the head, the spine and the autonomic and the peripheral nervous systems. That on the head, with 69 plates, comprises more than half the book. Comprehensive bibliographies are appended to the four sections. The publishing is excellent. This book should be in all reference collections on the nervous system.

Office Psychiatry: The management of the emotionally and mentally disturbed patient. By Louis G. Moench, M.D., assistant clinical professor of medicine and psychiatry, University of Utah School of Medicine. 8°, cloth, 310 pp., with 81 illustrations. Chicago: Year Book Publishers, Incorporated, 1952. $6.00.

This manual written especially for the general practitioner and the medical student covers the whole field of psychiatry from the development and growth of the personality, through the neuroses and psychoses to methods of treatment. Short lists of references are appended to the chapters, and there is an index. The publishing is good.

NOTICES

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held at the Mount Auburn Hospital on September 23, at 8 p.m. Dr. Samuel A. Levine will speak on the subject "Some Practical Points Concerning Auscultation of the Heart." All interested persons are cordially invited.

HARTFORD MEDICAL SOCIETY PROGRAM

The program for the fall series of lectures, to be held at 8:30 p.m. in the Hunt Memorial Building, 38 Prospect Street, Hartford, Connecticut, is presented below. All physicians are cordially invited.

October 5. Present Status of Medical vs. Surgical Treatment of Thyrotoxicosis. Dr. George Crile, Cleveland.

October 19. Clinical Application of Statistical Studies in Diabetes. Dr. Elliott P. Joslin, Boston.

November 2. Female Sex Hormones. Dr. Emil Novak, Baltimore.

November 16. Angina Pectoris and Its Treatment. Dr. Herrman L. Blumgart, Boston.

December 7. Criteria and Results of Cardiac Surgery in Children. Dr. Charles P. Bailey, Philadelphia.

December 21. Legal Aspects of Medical Practice. Mr. Cyril Coleman, Hartford.

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The eighteenth Annual Convention and Scientific Sessions of the National Gastroenterological Association will be held in Los Angeles, October 12-14. Immediately afterward (October 15-17) the fifth Annual Course in Postgraduate Gastroenterology will be held.

Further information concerning the program and details of the Postgraduate Course may be obtained from the Executive Officer, National Gastroenterological Association, 1819 Broadway, New York 23, New York.

VAN METER PRIZE AWARD

The Van Meter Prize Award of $300 and two honorable mentions are offered by the American Goiter Association for the best essays on original work on the thyroid gland. Essays must be submitted before January 15, 1954. The award will be presented at the annual meeting of the Association in Boston, April 29 through May 1, 1954. Further information may be obtained from Dr. John C. McClintock, Corresponding Secretary, 149½ Washington Avenue, Albany 10, New York.

ARTHRITIS AND RHEUMATISM FOUNDATION FELLOWSHIPS

Research fellowships in the basic sciences related to arthritis are being offered by the Arthritis and Rheumatism Foundation. Fellowships will be granted at both the predoctoral and postdoctoral levels. The predoctoral fellowships will range from $1500 to $3000 per year, the postdoctoral from $3000 to $6000. Senior fellowships for experienced investigation will range from $6000 to $7500, tenable for five years. Applications must be received before February 15, 1954. Further information may be obtained from the Medical Director, Arthritis and Rheumatism Foundation, 23 West 45th Street, New York 36, New York.

LICENSE FEE IN SOUTH DAKOTA

An annual registration fee of $2, effective January 1, 1954, for licensees in South Dakota has been announced by the South Dakota Board of Medical and Osteopathic Examiners. Licenses to practice medicine in South Dakota may be maintained by payment of the fee to the South Dakota Board of Medical Examiners, 300 First National Bank Building, Sioux Falls, South Dakota.

AMERICAN DERMATOLOGICAL ASSOCIATION ANNUAL PRIZE ESSAY CONTEST

A series of prizes for the best essays submitted for original work, not previously published, in dermatology or syphilology is offered by the American Dermatological Association. The prizes are $500, $300 and $200. Competition is open to scientists in general. Papers must be submitted not later than December 1, 1953. The paper winning first prize will be presented at the annual meeting of the American Dermatological Association, White Sulphur Springs, April 13 to 17, 1954. Further information may be obtained from the Secretary of the American Dermatological Association.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 18-21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.
SEPTEMBER 23. Middlesex South District Medical Society. Notice above.
SEPTEMBER 24-OCTOBER 1. Fourth Congress of Pan American Medical Women's Alliance. Page 124, issue of July 16.
OCTOBER 4-9. American Academy of Pediatrics. Page 1126, issue of June 25.
OCTOBER 5-DECEMBER 21. Hartford Medical Society Program. Notice above.
OCTOBER 12-14. National Gastroenterological Association. Notice above.
OCTOBER 12-17. Seventh International Congress of Pediatrics. Page 170, issue of July 23.
OCTOBER 15-17. Annual Course in Postgraduate Gastroenterology. Notice above.
OCTOBER 17-20. American Association of Blood Banks. Page 1126, issue of June 25.
OCTOBER 19-30. New York Academy of Medicine. Page xvii, issue of June 11.
OCTOBER 25-29. American Institute of Dental Medicine. Page 124, issue of July 16.
OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.
NOVEMBER 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.
DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.
MAY 31-JUNE 3, 1954. American Urological Association. Page xvii, issue of July 23.
SEPTEMBER 12-15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.
SEPTEMBER 16-18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX EAST

SEPTEMBER 23.
NOVEMBER 18.
JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 12. Annual Meeting. (Harlow Dinner.)

MIDDLESEX SOUTH

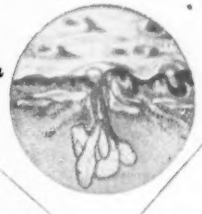
SEPTEMBER 23.

(*Notices concluded on page xiii*)

impetigo

skin infections and antibiotics

acne



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1. *Bednar, G. A.: South. M. J. 46:298 (March) 1953.*
2. *Wright, C. S. et al.: A. M. A. Arch. Dermat. & Syph. 67:125 (Feb.) 1953.*
3. *Robinson, H. M. et al.: South. M. J. (in press).*
4. *Andrews, G. C. et al.: J. A. M. A. 146:1107 (July 21) 1951.*

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NOTICES (*Concluded from page 260*)

Calendar of Boston District for the Week Beginning Thursday, August 13

Thursday, August 13

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
11:00 a.m.–12:00 m. Pediatric Conference, Mt. Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
5:00 p.m. Case Presentation and Pathological Discussion. Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

Friday, August 14

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

Saturday, August 15

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek, Stearns Auditorium, New England Center Hospital.

Monday, August 17

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m. Pediatric Medical-Surgical Conference (Boston Floating Hospital). Pratt Lecture Hall. Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

Tuesday, August 18

9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

Wednesday, August 19

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*Open to the medical profession.

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